A Novel Fragmentation Reaction of Avermectin Aglycons

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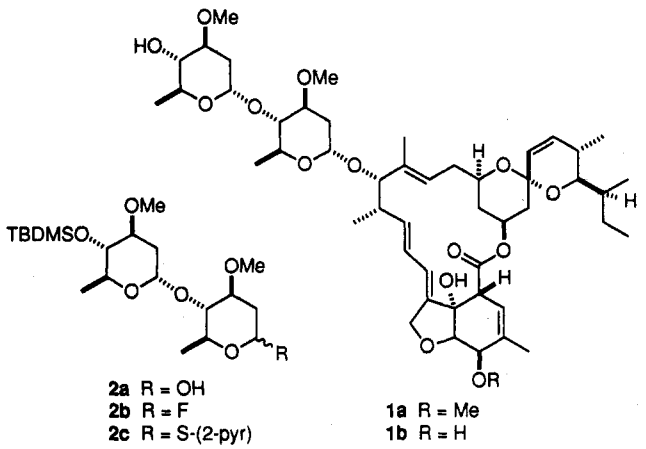
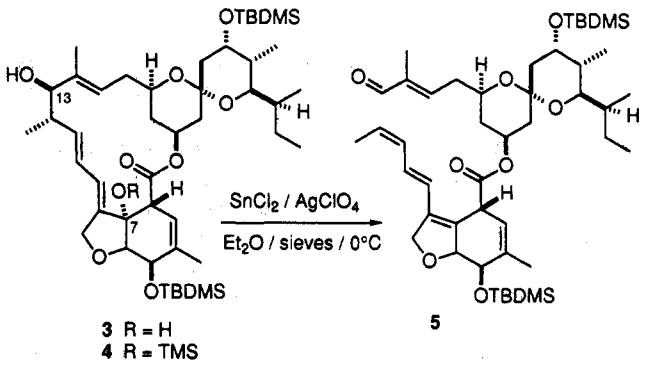
The avermectins are naturally occurring macrocyclic lactones with important anthelmintic and pesticidal activity.[1] The potent antiparasitic activity of the avermectins has generated considerable interest in the synthesis of these compounds.[2] These synthetic efforts have been highlighted by the total synthesis of avermectin A_{1a} (**1a**) by Danishefsky et al.[2a,b] and syntheses of avermectin



B_{1a} (**1b**) by Hanessian et al.[2c,d] and Ley et al.[2e] We have long been interested in novel avermectin analogs[3] and recently focused our efforts on the 13-*epi*-avermectins.[3a] During the course of this work we discovered and report herein a novel fragmentation reaction of avermectin aglycons.

The key step in our synthetic plan for 13-*epi*-avermectins involved glycosylation of a suitably protected 13-*epi*-avermectin aglycon with an activated avermectin disaccharide. The avermectin disaccharide unit (**2a**)[4a,b] is now readily available, and several activated avermectin disaccharides have also been reported.[2a-d,4c] Hanessian's pyridylthio glycoside derivative **2c**[2d] ultimately proved to be the most useful for our purposes. However, our initial studies centered on the reaction of protected 13-*epi*-avermectin B_{2a} aglycon **3**[3a] with glycosyl fluoride **2b**[4c] using a procedure analogous to the one used by Nicolaou et al.[4c] in their partial synthesis of avermectin B_1. We found that, in contrast to the clean reaction reported by Nicolaou for the reaction of **2b** with a protected avermectin B_1 aglycon (with the natural α stereochemistry at C-13), the reaction with 13-*epi*-avermectin B_{2a} aglycon **3** under these condi-



tions ($AgClO_4/SnCl_2$/ether/0 °C/3A sieves) afforded a mixture of several compounds with the desired glycosylation product present in low and variable yields (8-21%). Speculating that some of the side products were due to the presence of a free hydroxyl group at C-7 of **3**, we decided to repeat the reaction with a fully protected analog of **3**. Accordingly, we blocked the 7-OH as a trimethylsilyl ether (trimethylsilylation of both the C-13 and C-7 hydroxyl groups followed by selective hydrolysis of the secondary (C-13) trimethylsilyl ether) to afford fully protected 13-*epi*-avermectin B_2 aglycon **4**. In contrast to the results obtained with aglycon **3**, reaction of **4** with glycoside **2b** under the Nicolaou conditions proceeded cleanly and rapidly to afford one major product. Unfortunately, this was clearly *not* the desired glycosylation product since the NMR spectrum was devoid of signals associated with the disaccharide. The spectrum did, however, contain resonances for an additional olefinic proton as well as an aldehyde signal. This unanticipated product was identified by NMR[5] as triene aldehyde **5**. The ^1H and ^{13}C NMR assignments were made with the aid of COSY, NOESY, DEPT, and HETCOR NMR experiments. The geometries of the 9-10, 11-12, and 14-15 double bonds (avermectin numbering) were determined by a combination of ^1H NMR coupling constants and NOESY cross-peaks (Figure 1). Aldehyde **5** decomposed rapidly in the presence of acid but was only slightly unstable under

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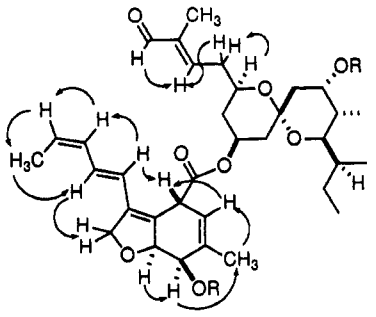
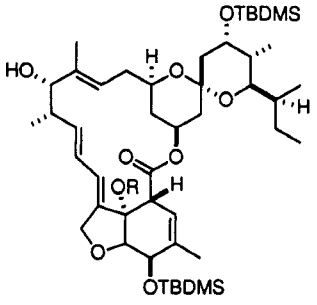


Figure 1. NOESY cross-peaks.

neutral conditions. As expected, **5** was completely inactive in our brine shrimp assay.[6]

Aldehyde **5** is probably derived from **4** by a vinylogous fragmentation–elimination reaction similar to the Grob fragmentation.[7] The novelty of this unexpected fragmentation reaction prompted us to examine it further. Control experiments in which various components of the reaction mixture were omitted demonstrated that disaccharide **2b** was not required for the reaction to occur but that both $AgClO_4$ and $SnCl_2$ were necessary.[8] The fragmentation reaction also occurred when **3** (free C-7 OH group) was treated with $AgClO_4$ and $SnCl_2$ (with no **2b** present) but was considerably slower and afforded more byproducts than the reaction of **4** (7-*O*-TMS) under the same conditions. Aldehyde **5** was likewise obtained when the corresponding 13-α (natural stereochemistry) aglycons **6** and **7** were subjected to the same reaction conditions.



6 R = H
7 R = TMS

The reaction is thus independent of the C-13 stereochemistry but is affected by the nature of the C-7 substituent.[9] We did not explore the effect of alternative anions on the reaction. However, we believe that it is the cations (Ag^+ and Sn^{2+}) which play the crucial role and that any nonnucleophilic counterion would suffice.

In conclusion, we have discovered a novel fragmentation reaction of avermectin aglycons. It is conceivable that this reaction may provide a useful source of avermectin aglycon fragments (especially the "northern" half) for biological or synthetic studies although we have not yet explored this possibility.

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(8) Similar fragmentation reactions have subsequently been observed by other Merck scientists under a variety of conditions. These results will be published separately.

(9) The presence of a 7-*O*-TMS ether also has a dramatic effect on the hydrolysis of an avermectin 8,9-epoxide: Blizzard, T. A.; Mrozik, H.; Fisher, M. H. *Tetrahedron Lett.* **1988**, *29*, 3163.

Experimental Section

^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ solution at 400 and 100 MHz, respectively, on a Varian XL-400 instrument. Chemical shifts are reported in δ units using the 7.24-ppm (^1H) and 77.0-ppm (^{13}C) resonances of residual chloroform as internal standards. Signal assignments were made with the assistance of ^1H–^1H correlation spectroscopy (COSY), ^1H–^{13}C correlation spectroscopy (HETCOR), 2-D NOE spectroscopy (NOESY), and distortionless enhancement by polarization transfer (DEPT). The NMR experiments were performed using standard Varian software. Mass spectra were measured on a Varian MAT 731 instrument. Elemental analyses were performed by the Merck analytical chemistry department or by Robertson Microlit Laboratories.

7-*O*-(Trimethylsilyl)-5,23-bis-*O*-(*tert*-butyldimethylsilyl)-13-*epi*-avermectin B_2 Aglycon (4). Bis(trimethylsilyl)trifluoroacetamide (BSTFA, 1.92 mL, 7.22 mmol) was added to a solution of 5,23-bis-*O*-(*tert*-butyldimethylsilyl)-13-*epi*-avermectin B_2 aglycon (**3**)[3a] (400 mg, 0.48 mmol) in 5 mL of dry DMF. The resulting solution was stirred at room temperature for 24 h, and then the solvent and excess reagent were removed under high vacuum. Analytical TLC showed incomplete reaction so the residue was dissolved in 5 mL of dry DMF, and then 2.5 mL (9.4 mmol) of BSTFA was added. The resulting solution was stirred at room temperature for 69 h, and then the solvent and excess reagent were removed under high vacuum. Analytical TLC showed complete reaction. The crude 7,13-bis-*O*-(trimethylsilyl)-5,23-bis-*O*-(*tert*-butyldimethylsilyl)-13-*epi*-avermectin B_2 aglycon thus obtained was dissolved in 4 mL of 9:1 tetrahydrofuran/water, and then *p*-toluenesulfonic acid (20 mg, 0.10 mmol) was added. The resulting solution was stirred at room temperature for 20 min and then partitioned between ether (5 mL) and 5% aqueous $NaHCO_3$ (3 mL). The aqueous layer was extracted with ether (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to a yellow oil (680 mg). This crude product was purified by flash chromatography on silica gel eluted with 6.25% acetone in hexane to afford 242 mg (79%) of **4** (R_f 0.23) as a white foam. Selected ^1H NMR data: (400 MHz, $CDCl_3$) δ 5.80 (1 H, dd, J = 15, 11 Hz, H_{10}), 5.62 (1 H, dt, J = 11, 2 Hz, H_9), 5.44 (1 H, br s, H_3), 5.30 (1 H, dd, J = 15, 10 Hz, H_{11}), 5.31–5.25 (1 H, m, H_{15}), 4.74 (1 H, tt, J = 11, 5 Hz, H_{19}), 4.64 and 4.54 (2 × 1 H, 2 dd, J = 14, 2 Hz, H_{8a}), 4.36 (1 H, m, H_5), 3.82–3.75 (2 H, m, H_6 and H_{23}), 3.74 (1 H, d, J = 10 Hz, H_{13}), 3.67 (1 H, d, J = 10 Hz, H_{25}), 3.19 (1 H, br s, H_2), 2.42–2.32 (1 H, m, H_{12}), 1.76 (3 H, br s, H_{4a}), 1.57 (3 H, s, H_{14a}), 1.14 (3 H, d, J = 7 Hz, H_{12a}), 0.90 (9 H, s, Si^{t}Bu), 0.86 (9 H, s, Si^{t}Bu), 0.09 (9 H, s, $Si(CH_3)_3$). ^{13}C NMR data: (100 MHz, $CDCl_3$) δ 170.7, 140.4, 139.8, 138.3, 134.2, 124.1, 123.7, 121.0, 120.3, 97.6, 83.6, 83.4, 80.7, 77.3, 70.1, 69.4, 69.1, 67.3, 47.2, 42.3, 41.5, 36.3, 36.0, 35.4, 34.6, 27.3, 25.9, 20.0, 19.3, 18.4, 18.1, 14.0, 12.3, 11.6, 10.5, 2.3, −4.4, −4.5, −4.7, −5.0. FAB MS: *m/e* 909 (M + Li). Anal. Calcd for $C_{49}H_{86}O_9Si_3$: C, 65.14; H, 9.59. Found: C, 65.23; H, 9.65.

Fragmentation Product 5. Molecular sieves (3A, ca. 300 mg) were added to a solution of aglycon **4** (50 mg, 0.055 mmol) in 1 mL of dry ether. The resulting mixture was cooled to 0 °C, and then $SnCl_2$ (13 mg, 0.069 mmol) and $AgClO_4$ (14 mg, 0.069 mmol) were added sequentially. The reaction mixture was stirred at 0 °C for 15 min and then centrifuged. The supernatant was added to 5% aqueous $NaHCO_3$ (2 mL), and the layers were separated. The aqueous layer was extracted with ether (2 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated to a yellow oil. The crude product was purified by preparative TLC on a 0.5-mm silica gel plate eluted with 9% acetone in hexane to afford 31 mg of **5** (R_f 0.53) as a light yellow oil (ca. 95% pure). This material was further purified by preparative TLC on a 0.5-mm silica gel plate eluted with 16% ether in hexane to afford 29 mg (64%) of **5** (R_f 0.45) as a light yellow oil. ^1H NMR: (400 MHz, $CDCl_3$) δ 9.38 (1 H, s, H_{13}), 6.64 (1 H, br t, J = 6 Hz, H_{15}), 6.35 (1 H, d, J = 15 Hz, H_9), 6.22 (1 H, dd, J = 11, 15 Hz, H_{10}), 6.04 (1 H, tq, J = 11, 2 Hz, H_{11}), 5.55 (1 H, dq, J = 11, 7 Hz, H_{12}), 5.46 (1 H, br s, H_3), 5.09 (1 H, tt, J = 11, 5 Hz, H_{19}), 4.90–4.80 (3 H, m, H_8 and H_{8a}), 4.10 (1 H, br s, H_2), 4.04 (1 H, d, J = 4 Hz, H_5), 3.84–3.76 (2 H, m, H_{23} and H_{17}), 3.63 (1 H, dd, J = 10, 2 Hz, H_{25}), 2.47 (2 H, t, J = 6 Hz, H_{16}), 1.94 (1 H, dd, J = 11, 5 Hz, H_{20eq}), 1.96–1.88 (1 H, m, H_{18eq}), 1.85 (1

H, dd, J = 14, 3 Hz, H_{22eq}), 1.80 (3 H, br s, H_{4a}), 1.75 (3 H, dd, J = 7, 2 Hz, H_{12a}), 1.69 (3 H, s, H_{14a}), 1.60–1.52 (1 H, m, H_{24}), 1.55 (1 H, dd, J = 14, 6 Hz, H_{22ax}), 1.42–1.35 (1 H, m, H_{26}), 1.38 (1 H, t, J = 12 Hz, H_{20ax}), 1.35–1.25 (2 H, m, H_{27}), 1.19 (1 H, dt, J = 11, 11 Hz, H_{18ax}), 0.85 (9 H, s, Si^{t}Bu), 0.81 (9 H, s, Si^{t}Bu), 0.90–0.80 (6 H, obsc. H_{24a} and H_{26a}), 0.77 (3 H, t, J = 6 Hz, H_{28}), 0.09 (3 H, s, $SiCH_3$), 0.07 (3 H, s, $SiCH_3$), 0.01 (3 H, s, $SiCH_3$), 0.00 (3 H, s, $SiCH_3$). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 195.2 (C-13), 170.3 (C-1), 150.8 (C-15), 140.1, 137.9, 132.4, 129.6 (C-11), 128.0 (C-12), 127.3, 125.9 (C-10), 121.9 (C-9), 120.2 (C-3), 97.7 (C-21), 86.2 (C-6), 76.1 (C-8a), 71.5 (C-5), 70.7 (C-25), 69.4 (C-23), 69.0 (C-19), 66.4 (C-17), 43.2 (C-2), 42.3 (C-22), 41.5 (C-20), 36.2 (C-24), 36.1 (C-18), 35.3 (C-26), 34.9 (C-16), 27.5 (C-27), 25.9 (SiC-(CH_3)$_3$), 25.8 (SiC(CH_3)$_3$), 22.4 (C-4a), 18.2 (SiC(CH_3)$_3$), 18.1 (SiC(CH_3)$_3$), 14.0 (C-28), 13.7 (C-12a), 12.3 (C-24a or C-26a), 11.4 (C-24a or C-26a), 9.3 (C-14a), −4.3 ($SiCH_3$), −4.4 ($SiCH_3$), −4.6 ($SiCH_3$), −4.9 ($SiCH_3$). FAB MS: m/e 819 (M + Li). HR-FAB MS: m/e calcd for $C_{46}H_{76}O_8Si_2Li$ 819.5238, found 819.5255 (M + Li).

7-*O*-(Trimethylsilyl)-5,23-bis-*O*-(*tert*-butyldimethylsilyl)avermectin B_2 Aglycon (7). Bis(trimethylsilyl)trifluoroacetamide (BSTFA, 1.44 mL, 5.41 mmol) was added to a solution of 5,23-bis-*O*-(*tert*-butyldimethylsilyl)avermectin B_2 aglycon (**6**)[3a] (300 mg, 0.36 mmol) in 4 mL of dry DMF. The resulting solution was stirred at room temperature for 64 h, and then the solvent and excess reagent were removed under high vacuum. The crude 7,13-bis-*O*-(trimethylsilyl)-5,23-bis-*O*-(*tert*-butyldimethylsilyl)avermectin B_2 aglycon thus obtained was dissolved in 4 mL of 9:1 tetrahydrofuran/water, and then *p*-toluenesulfonic acid (20 mg, 0.10 mmol) was added. The resulting solution was stirred at room temperature for 1 h and then worked up as described above to afford a yellow oil (250 mg). The crude product was purified by flash chromatography on silica gel eluted with 6.25% acetone in hexane to afford 141 mg (43%) of **7** (R_f 0.22) as a colorless oil. Selected ^1H NMR data: (300 MHz, $CDCl_3$) δ 5.82–5.60 (3 H, m, H_9 and H_{10} and H_{11}), 5.45–5.35 (2 H, m, H_3 and H_{15}), 4.76 (1 H, tt, J = 11, 5 Hz, H_{19}), 4.64 and 4.53 (2 × 1 H, 2 dd, J = 14, 2 Hz, H_{8a}), 4.36 (1 H, br s, H_5), 4.03 (1 H, br s, H_{13}), 3.80–3.65 (4 H, m, H_6 and H_{17} and H_{23} and H_{25}), 3.19 (1 H, br s, H_2), 1.75 (3 H, br s, H_{4a}), 1.60 (3 H, s, H_{14a}), 1.18 (3 H, d, J = 7 Hz, H_{12a}), 0.91 (9 H, s, Si^{t}Bu), 0.86 (9 H, s, Si^{t}Bu), 0.09 (9 H, s, Si(CH_3)$_3$). FAB MS: m/e 909 (M + Li). Anal. Calcd for $C_{49}H_{86}O_9Si_3$: C, 65.14; H, 9.59. Found: C, 65.07; H, 9.58.

Acknowledgment. We thank Dr. L. Colwell for mass spectral data and Dr. Phil Eskola and Mr. Joe Leone for technical assistance.

Supplementary Material Available: ^1H, ^{13}C, and DEPT NMR spectra of **5** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.