Syntheses of 4″-*epi*-Amino-4″-deoxyavermectins B_1

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A practical synthesis of 4″-*epi*-aminoavermectins is described. High-yielding imine formation from 4″-oxo-5-*O*-(allyloxycarbonyl)avermectin B_1 (**5a**) was effectively accomplished using hexa- or heptamethyldisilazane/zinc chloride. Subsequent reduction with sodium borohydride provided the 4″-*epi*-amines **10a,b** and **12**, respectively, in 85–90% yields from ketone. Synthesis of ketone **5a** was accomplished by highly selective and high-yielding monoprotection of avermectin B_1 (**3**) to afford the C_5-allylcarbonate **4** followed by oxidation of the $C_{4''}$-hydroxyl (phenyl dichloro phosphate, DMSO, and TEA). Reductive amination was followed by removal of the allyl carbonate protecting group with $(Ph_3P)_4Pd(0)$–$NaBH_4$. Acidic methanol removal of the C_7-OH trimethylsilyl groups, followed by crystallization as the benzoic acid salts, gave the desired 4″-*epi*-(methylamino)-4″-deoxyavermectin B_1 benzoate (**1c**, MK-244, emamectin benzoate) or 4″-*epi*-amino-4″-deoxyavermectin B_1 benzoate (**14b**), respectively, in 60% overall yields.

Introduction

The avermectins form a class of highly functionalized pentacyclic natural products containing a 16-membered macrocyclic lactone, a spirocyclic ketal, and a 4-(α-L-oleandrosyl)-α-L-oleandrose disaccharide group attached at the C_{13}-OH position, and are prepared by fermentation with the avermectin-producing strain of *Streptomyces avermitilis*. They are among the most potent naturally occurring anthelmintic, insecticidal, and acaricidal compounds known.

The antiparasitic activity of the avermectins[1] toward a host of both endo- and ecto-parasites has been successfully commercialized in animals and in crop protection, as exemplified by "abamectin" (avermectin B_1) and "ivermectin".[2] This has stimulated the search for newer, novel, and more potent avermectin derivatives. Recently, a new class of aminoavermectins was reported which demonstrated considerably improved insecticidal activity against neonate *Spodoptera eriidania* larvae.[3] Among the members of this new class, 4″-*epi*-(methylamino)-4″-deoxyavermectin B_1 (**1a**) was shown to be one of the most effective reported, with a 1500-fold increase in potency vs avermectin B_1 (AVM B_1) against the beet armyworm *Spodoptera exigua* in a diet incorporation assay.[4a] Other studies have shown the hydrochloride salt (**1b**, MK-243)[5] to be effective against a wide variety of lepidoptera,[4a] spider mites,[4b] aphids,[4b] ticks,[4b] and other agricultural pests.[4c] Likewise, 4″-*epi*-amino-4-deoxyavermectin B_1 (**14a**, L-653,649)[3a–c] and its N-acetylated derivative (**2**, MK-397)[3d] (Figure 1) have also shown interesting anthelmintic activity.

This paper discusses the preparation of two closely related derivatives: 4″-*epi*-(methylamino)-4″-deoxyavermectin B_1 benzoate (**1c**, MK-244, emamectin benzoate), and 4″-*epi*-(acetylamino)-4″-deoxyavermectin B_1 (**2**, MK-397) and highlights the use of disilazane-mediated reductive amination chemistry for the introduction of amine functionality to the avermectins. By contrast, traditional reductive amination reaction conditions failed to complete imine formation and led to epimerization at the base-sensitive C_2 position. This synthesis began with a highly selective protection of the C_5-hydroxyl group of avermectin B_1 in a nonchlorinated solvent by the use of TMEDA with allyl chloroformate and ended with its efficient deprotection in the presence of an amine group using $(Ph_3P)_4Pd(0)$–$NaBH_4$. This work provides the basis for an efficient large scale synthesis of these potent second generation avermectins.

Results and Discussion

Among the variety of methods available for the conversion of equatorial cyclohexanols to axially configured cyclohexylamines, reduction of an intermediary imine still remains prominent.[6] In the case of our targeted aminoavermectins, **1** and **2**, preparation of an appropriately protected 4″-oxoavermectin derivative serves as a common intermediate to both. Protection of the C_5-hydroxy group of AVM B_1 (**3**) in the presence of the C_7 and $C_{4''}$-hydroxyl groups, using *tert*-butyldimethylsilyl chloride[3a] (TBDMSCl) and imidazole, optimally gave an 87:13 ratio of mono:bis (5: 4″,5) protected AVM B_1, with no reaction at the highly hindered C_7-hydroxyl group. As an alternative to silicon-based protecting groups, the

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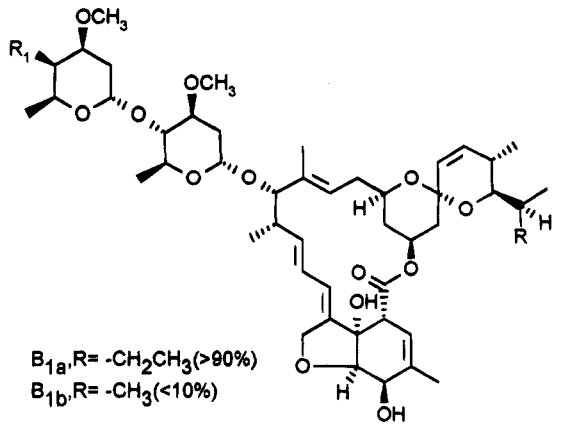
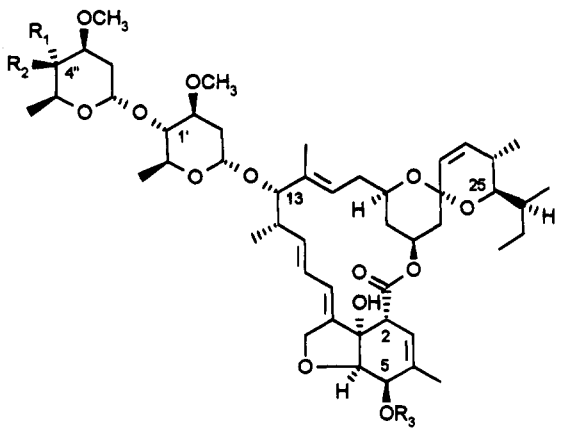


1a: R_1=CH_3NH; **1b**: R_1=$CH_3NH{\cdot}HCl$ [MK-243];
1c: R_1=$CH_3NH{\cdot}HCO_2Ph$ [MK-244]
2: R_1=CH_3CONH [MK-397]

Figure 1. MK-244 and MK-397.

Scheme 1. Protection and Oxidation[a]



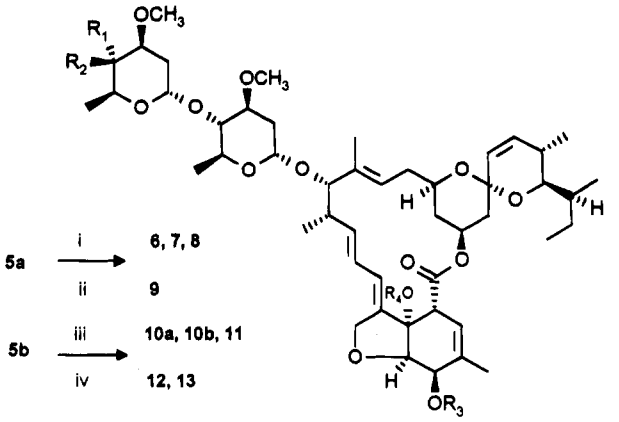
i ↔ **3**: R_1=OH, R_2=H, R_3=H
4: R_1=OH, R_2=H, R_3=$CO_2CH_2CH{=}CH_2$
5a: R_1=R_2=O, R_3=$CO_2CH_2CH{=}CH_2$ ↔ ii

[a] Key: (i) MTBE, TMEDA, allyl chloroformate; (ii) $PhOPOCl_2$, TEA, DMSO, IPAC.

selective acylation[7] with allyl chloroformate[8] was explored. The reaction of allyl chloroformate/triethylamine with AVM B_1 (**3**) to prepare the mono protected avermectin **4** (Scheme 1) showed chemosensitivity to the solvent chosen as the reaction vehicle. In THF and ethyl acetate poor selectivity resulted (~50:50, mono:bis), but chlorinated solvents (methylene chloride, 1,1,1-trichloroethane) produced product ratios of 93:7 (mono:bis). A remarkable increase in selectivity in nonchlorinated solvent was observed when *N,N,N′,N′*-tetramethyl-1,2-ethylenediamine (TMEDA) was substituted for TEA. In THF or *tert*-butyl methyl ether (MTBE) the mono:bis ratio of protected avermectins increased from 50:50 to 97:3.

Oxidation of 5-*O*-(allyloxycarbonyl) (AOC) AVM B_1 (**4**) was smoothly accomplished using the phenyl dichloro phosphate (PDCP)-mediated Pfitzner–Moffat oxidation[9] in methylene chloride or in nonchlorinated solvents like isopropyl acetate (*i*-PrOAc) to afford ketone **5a** (Scheme 1) in 90% yield.

Scheme 2. Reductive Amination and Deprotection[a]



5a —i→ **6, 7, 8**; —ii→ **9**
5b —iii→ **10a, 10b, 11**; —iv→ **12, 13**

5b: R_1=R_2=O, R_3=TBDMS, R_4=H
6: R_1=H, R_2=CH_3NH, R_3=TBDMS, R_4=H
7: R_1=CH_3NH, R_2=H, R_3=TBDMS, R=H
8: R_1=CN, R_2=CH_3NH, R_3=TBDMS, R_4=H
9: R_1=H, R_2=NH_2, R_3=TBDMS, R_4=H
10a: R_1=H, R_2=NH_2, R_3=$CO_2CH_2CH{=}CH_2$, R_4=H
10b: R_1=H, R_2=NH_2, R_3=$CO_2CH_2CH{=}CH_2$, R_4=TMS
11: R_1=NH_2, R_2=H, R_3=$CO_2CH_2CH{=}CH_2$, R_4=H
12: R_1=H, R_2=CH_3NH, R_3=$CO_2CH_2CH{=}CH_2$, R_4=TMS —v→ **1a**
13: R_1=CH_3NH, R_2=H, R_3=$CO_2CH_2CH{=}CH_2$, R_4=TMS
14a: R_1=H, R_2=NH_2, R_3=R_4=H —vi→ **2**
14b: R_1=H, R_2=$NH_2{\cdot}HCO_2Ph$, R_3=R_4=H
15: R_1=H, R_2=$N[CH_3]CH_2CH{=}CH_2$, R_3=R_4=H

[a] Key: (i) CH_3NH_2, HOAc, $NaCNBH_3$; (ii) NH_3, HOAc, $NaCNBH_3$; (iii) HxMDS, $ZnCl_2$, i-PrOAc; EtOH, $NaBH_4$; (iv) HpMDS, $ZnCl_2$, i-PrOAc; EtOH, $NaBH_4$; (v) $Pd(Ph_3P)_4(0)$, MeOH, $NaBH_4$; H^+; (vi) Ac_2O, i-PrOAc.

Reductive amination of 4″-oxo-5-*O*-TBDMS AVM B_1 (**5b**) (CH_3NH_2/HOAc in THF and $NaCNBH_3$ in ethanol)[3a] gave rise to a complex mixture (Scheme 2) containing the desired 4″-*epi*-CH_3NH-5-*O*-TBDMS AVM B_1 (**6**) (50%), the isomeric 4″-CH_3NH-5-*O*-TBDMS AVM B_1 (**7**) (10%), 4″-CN-4″-CH_3NH-5-*O*-TBDMS AVM B_1 (**8**) (10%), and an epimeric mixture of 4″-hydroxy AVM B_1 (20–30%, resulting from incomplete imine formation). Epimerization at the C_2 position (5–20%) also occurred during the course of the reaction, with greater amounts present in samples that were aged longer or at higher temperatures during imine formation. Imine reduction with $NaBH_4$ increased the stereoselectivity of hydride addition and eliminated the cyanoamine byproduct to give amine **6** in 65% yield, but C_2 epimerization and incomplete imine formation remained as the major sources of yield loss.

Similar reductive amination studies using ammonium acetate/$NaBH_4$ to make 4″-*epi*-NH_2-5-*O*-TBDMS AVM B_1 (**9**) gave maximized yields of 25%, with the greatest loss occurring from incomplete imine formation. The use of stronger acid (ammonium chloride), molecular sieves, or a variety of Lewis acids failed to significantly influence the outcome.

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An alternative to the thermodynamically controlled dehydration step involved in imine formation with ammonia was achieved by the use of hexamethyldisilazane (HxMDS) with a Lewis acid.[6d,10] The reaction of ketone **5a** with HxMDS/$ZnCl_2$ in *i*-PrOAc followed by the addition of $NaBH_4$ and EtOH (Scheme 2) resulted in an 84% overall yield of 4″-*epi*-amino products **10a** (56%) and **10b** (28%) along with a minor amount of the isomeric amine **11**, with less than 3% ketone reduction products and no detectable epimerization at the labile C_2 position. Silylated byproduct **10b** is formed from **10a** under the reaction conditions in variable yield depending on the temperature, age period, and the amount of excess HxMDS present. This byproduct is readily deprotected along with **10a** and converted into the same aminoavermectin, **14a**.

Imine formation using heptamethyldisilazane (HpMDS)/$ZnCl_2$ on ketone **5a**, followed by reduction with $NaBH_4$, resulted in an 81% yield of methylamine derivative **12**, along with a minor amount of **13** (Scheme 2) with the same degree of control of imine formation and absence of C_2 epimerization as demonstrated in the preparation of **10a,b**.

While imine formation with HxMDS or HpMDS was sluggish with $ZnCl_2$ unless a stoichiometric amount was employed at 50 °C, a significant rate acceleration was achieved using $Zn(OCOCF_3)_2$, which could be used in catalytic (10 mol %) quantities.

Methods for the removal of AOC-protecting groups include: PtO_2 or Pd–C/H_2,[7] sodium/ammonia,[7] phosphonium iodide,[7] nickel carbonyl,[11] and soluble palladium(0)-catalyzed cleavage in conjunction with a variety of nucleophiles.[12] Attempts to use $(Ph_3P)_4Pd(0)$ with formic acid[12f] as the nucleophile led to significant amounts (5–20%) of N-allylated byproduct **15**.[12a,f] Deprotection of **10a,b** or **11** using sodium borohydride[13,14] in ethanol with $(Ph_3P)_4Pd(0)$ reductively trapped the reactive palladium intermediate, resulting in the complete elimination of the N-allylation. Subsequent removal of the 7-*O*-TMS groups in acidified ethanol solution was followed by crystallization of **1a** or **14a** as their benzoic acid salts (**1c** and **14b**, respectively). The final preparation of MK-397 (**2**) was accomplished by acylation of aminoavermectin **14a** (or its benzoate salt **14b**) with acetic anhydride and crystallization from acetonitrile.

This work has demonstrated several important features in aminoavermectin chemistry: a highly selective monoprotection of the C_5-hydroxyl group of avermectin B_1 with allyl chloroformate in the presence of TMEDA; a high-yielding reductive amination of a 4″-ketone by conversion to an imine using disilazanes/$ZnCl_2$ followed by reduction with $NaBH_4$; and the use of $(Ph_3P)_4Pd(0)$–$NaBH_4$ to remove an allyloxy carbonate protecting group in the presence of an amine group avoiding the formation of *N*-allyl byproducts. All of these features have been combined to give a high-yielding nonchromatographic route to crystalline MK-244 (**1c**) and MK-397 (**2**) and provides the basis of large scale preparation of their intermediates and products.

Experimental Section

General. HPLC analyses were performed using a Spectra-Physics SP8700 ternary solvent delivery system, a Vydac C18 protein/peptide column (5 mm particle size, 4.6 × 150 mm) reversed-phase column, solvent system A:B (acetonitrile:water, with 0.1 vol % TFA in each) at 25 °C, 3.0 mL/min, with UV detection at 245 nm. Samples of each product were isolated and purified by column chromatography (E. Merck silica gel 60, 230–400 mesh ASTM using ethyl acetate:hexanes mixtures) for characterization. All reactions were carried out under an atmosphere of N_2, and the following solvents and reagents were dried (where needed) over 3 Å or 4 Å molecular sieves prior to use: MTBE, THF, EtOH, *i*-PrOAc, TEA, TMEDA, DMSO, and MeOH. Other solvents and reagents were used as received. Karl Fisher water analyses of reaction mixtures and solvents were carried out on a Metrohm 684 KF Coulometer and were generally in the 50–100 μg/mL range. Infrared spectra were recorded on a Perkin-Elmer 1420 ratio recording infrared spectrophotometer. Melting points were determined using a DuPont 9900 DSC (2 °C/min, under N_2 in an open cup) and are reported as a range from the DSC extrapolated onset temperature to the peak temperature. Proton and carbon-13 spectra were recorded in $CDCl_3$ on a Bruker AM-400 at a frequency of 400.13 and 100.16 MHz, respectively. The chemical shifts are reported in ppm relative to residual $CHCl_3$ for proton (δ = 7.27 ppm) and $CDCl_3$ for carbon (δ = 77.0 ppm). All coupling constants are reported in Hz, and the following proton multiplicites are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = mulitiplet, om = overlapping multiplets, br = broad. High-resolution mass spectroscopy studies were performed in the FAB mode. Avermectin B_1 was used as the mixture of B_{1a} and B_{1b} components available as "abamectin".

5-*O*-(Allyloxycarbonyl)avermectin B_1 (4). Allyl chloroformate (5.50 mL, 51.6 mmol) in MTBE (15 mL) was added dropwise over 20 min to a solution of avermectin B_1 (**3**) (39.1 g, 44.9 mmol) and TMEDA (5.20 g, 44.9 mmol) in MTBE (200 mL) at −15 °C to give a white precipitate. The reaction mixture was aged for 1.5 h at −10 to −15 °C and then poured into 2% aqueous H_3PO_4 (125 mL). The organic phase was separated and evaporated *in vacuo* to give **4** as a solid white foam (52.4 g). HPLC assay: gradient, solvent A:B = 65:35 to 75:25 over 15 min; results: 4 (B_{1b}: t_R = 6.1 min; 3.5 g, 3.7 mmol; B_{1a}: t_R = 7.8 min; 38.3 g, 40.0 mmol); yield = 97% (vs a wt % standard). ^1H NMR: δ 5.94 (ddt, J = 17.1, 10.4, 5.8, 1H), 5.85 (m, 1H), 5.78–5.71 (om, 3H), 5.57 (br s, 1H), 5.55 (dd, J = 10.0, 2.7, 1H), 5.42–5.34 (om, 4H), 5.27 (m, 1H), 4.99 (m, 1H), 4.77 (d, J = 3.0, 1H), 4.70–4.66 (om, 3H), 4.61 (dd, J = 14.3, 2.1, 1H), 4.12 (d, J = 6.0, 1H), 3.99 (s, OH), 3.93 (br s, 1H), 3.88–3.80 (om, 2H), 3.77 (dq, J = 9.4, 6.3, 1H), 3.62 (m, 1H), 3.51–3.45 (om, 2H), 3.43 (S, 3H), 3.42 (s, 3H), 3.37 (q, J = 2.3, 1H), 3.24 (t, J = 9.0, 1H), 3.16 (br t, J = 9.2, 1H), 2.58 (d, J = 1.5, OH), 2.52 (m, 1H), 2.35–2.20 (om, 5H), 2.02 (dd, J = 7.4, 1.4, 1H), 1.81 (br s, 3H), 1.81–1.76 (om, 1H), 1.62–1.45 (om, 6H), 1.49 (s, 3H), 1.27 (d, J = 6.3, 3H), 1.25 (d, J = 6.3, 3H), 1.16 (d, J = 6.9, 3H), 0.96–0.87 (om, 10H). ^{13}C NMR:

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(14) Using $(Ph_3P)_4Pd(0)$–$NaCNBH_3$, the cyclic allylic carbonate derivative of a *cis*-1,2-dihydroxy-3-cyclohexene was easily cleaved, but the corresponding diethyl carbonates were reported to be inert to the reaction conditions: Sutherland, J. K.; Tometzki, G. B. *Tetrahedron Lett.* **1984**, *25*, 881.

δ 173.5, 154.9, 139.3, 138.1, 136.3, 135.2, 133.1, 131.5, 127.8, 124.8, 121.6, 120.4, 118.7, 118.3, 98.5, 95.8, 94.9, 81.9, 80.9, 80.4, 79.4, 78.2, 77.5, 76.1, 74.9, 73.6, 68.8, 68.6, 68.5, 68.4, 68.1, 67.3, 56.5, 56.4, 45.8, 40.5, 39.8, 36.6, 35.2, 34.5, 34.2_6, 34.2_3, 30.6, 27.5, 20.2, 19.7, 18.4, 17.7, 16.4, 15.1, 13.0, 12.1. IR (CCl_4) λ_{max}: 3500, 3480, 1745, 1715, 1460, 1370, 1290, 1260, 1160, 1100, 1065, 990 cm^{-1}. HRMS: $[M + Li]^+$ = 963.5302 (calcd = 963.5292).

4″-Oxo-5-*O*-(allyloxycarbonyl)avermectin B_1 (5a). A solution of $PhOPOCl_2$ (7.7 mL, 52.0 mmol) in *i*-PrOAc (15 mL) was added dropwise over 1 h to a solution of 5-*O*-AOC AVM B_1 (**4**) (29.7 g, 30.6 mmol by assay), DMSO (8.7 mL, 122 mmol), and TEA (21.3 mL, 153 mmol) in *i*-PrOAc (160 mL) at −15 °C. The mixture was aged for 1 h at −15 °C and then poured into 1% aqueous H_3PO_4. The aqueous phase was extracted with *i*-PrOAc (3 × 50 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (50 mL) and evaporated *in vacuo* to give **5a** as a yellowish solid (37.6 g). HPLC assay: sample preparation,[15] 40.0 mg of crude ketone in 0.5 mL EtOH was treated with 4 mg of $NaBH_4$ for 2 min to give a mixture of $C_{4''}$-OH epimers and then diluted to 100 mL with acetonitrile; gradient, solvent A:B = 65:35−75:25 over 15 min; results (4″-*epi*-OH B_{1b}: t_R = 5.4 min; 1.77 g, 1.87 mmol; B_{1a}: t_R = 6.80 min, 19.2 g, 20.1 mmol; 4″-OH B_{1b}: t_R = 6.0 min, 0.42 g, 0.44 mmol; B_{1a}: t_R = 7.8 min, 4.99 g, 5.2 mmol; total = 27.6 mmol); assay yield = 90% (vs a wt % standard). ^1H NMR: δ 5.94 (ddt, *J* = 17.1, 10.4, 5.6, 1H), 5.86 (m, 1H), 5.78−5.72 (om, 3H), 5.57−5.53 (om, 2H), 5.40−5.34 (om, 4H), 5.26 (m, 1H), 5.00 (m, 1H), 4.80 (br d, *J* = 2.8, 1H), 4.70−4.65 (om, 3H), 4.61 (dd, *J* = 14.2, 2.0, 1H), 4.42 (q, *J* = 6.6, 1H), 4.20 (dd, *J* = 11.7, 6.4, 1H), 4.12 (d, *J* = 6.1, 1H), 4.00 (s, OH), 3.94 (br s, 1H), 3.93−3.83 (om, 2H), 3.68 (m, 1H), 3.51 (s, 3H), 3.49 (dd, *J* = 10.1, 1.3, 1H), 3.45 (s, 3H), 3.38 (q, *J* = 2.2, 1H), 3.33 (t, *J* = 8.8, 1H), 2.58 (ddd, *J* = 12.8, 6.4, 1.8, 1H), 2.53 (m, 1H), 2.32−2.23 (om, 4H), 2.13 (m, 1H), 2.02 (dd, *J* = 9.2, 2.9, 1H), 1.82 (br s, 3H), 1.81−1.76 (om, 1H), 1.64−1.46 (om, 5H), 1.50 (s, 3H), 1.28 (d, *J* = 6.6, 3H), 1.27 (d, *J* = 6.2, 3H), 1.17 (d, *J* = 6.9, 3H), 0.97−0.91 (om, 9H), 0.88 (m, 1H). ^{13}C NMR: δ 205.9, 173.5, 154.9, 139.4, 137.9, 136.3, 135.1, 133.2, 131.5, 127.8, 124.9, 121.5, 120.4, 118.7, 118.4, 98.1, 95.8, 95.0, 82.1, 81.3, 80.9, 79.2, 78.1, 77.5, 74.9, 73.6, 70.8, 68.8, 68.5_3, 68.5_0, 68.4, 67.0, 58.3, 56.5, 45.8, 40.9, 39.7, 39.5, 36.6, 35.2, 34.6, 34.3, 30.6, 27.5, 20.3, 19.7, 18.4, 16.4, 15.1, 13.9, 13.0, 12.1. IR (CCl_4) λ_{max}: 3460, 2990, 2940, 1750, 1718, 1455, 1375, 1270, 1205, 1165, 1130, 1060, 990 cm^{-1}. HRMS: $[M + Li]^+$ = 961.5144 (calcd = 961.5136).

4″-*epi*-Amino-5-*O*-(allyloxycarbonyl)-4″-deoxyavermectin B_1 (10a,b). A mixture of crude ketone **5a** (26.3 g, 27.5 mmol by assay), hexamethyldisilazane (15.3 g, 94.7 mmol), and $ZnCl_2$ (4.16 g, 30.5 mmol) in *i*-PrOAc (135 mL) was warmed to 50 °C, aged for 4 h, and then cooled to 5 °C. $NaBH_4$ (3.25 g, 85.9 mmol) and EtOH (50 mL) were added, while the temperature was maintained at <10 °C, and the mixture was aged for 1 h at 20 °C. The mixture was treated dropwise with 10% aqueous acetic acid (100 mL) and aged for 15 min. The pH of the mixture was adjusted to 8.0 with 5 N aqueous NaOH and the precipitated zinc salts were filtered. The aqueous phase was extracted with *i*-PrOAc (3 × 50 mL), and the combined organic phases were evaporated *in vacuo* to give **10a,b** as a yellowish solid (37.2 g). HPLC assay: gradient, solvent A:B = 50:50−85:15 over 20 min; results: **10a** (t_R: B_{1b} = 7.0 min, B_{1a} = 8.0 min; 14.7 g, 15.4 mmol); **10b** (t_R: B_{1b} = 11.6 min; B_{1a} = 12.0 min; 7.9 g, 7.7 mmol); **14** (t_R: B_{1b} = 2.7 min; B_{1a} = 3.1 min; 0.5 g, 0.6 mmol); **11** (t_R: B_{1b} = 7.4 min; B_{1a} = 8.8 min; 1.1 g, 1.2 mmol); assay yield = 86% (vs a wt % standard).

10a. ^1H NMR: δ 5.94 (ddt, *J* = 17.2, 10.5, 5.8, 1H), 5.85 (m, 1H), 5.77−5.01 (om, 3H), 5.57 (br s, 1H), 5.54 (dd, *J* = 9.9, 2.6, 1H), 5.42−5.34 (om, 4H), 5.26 (m, 1H), 4.98 (m, 1H), 4.77 (d, *J* = 3.1, 1H), 4.70−4.58 (om, 4H), 4.12 (d, *J* = 6.1, 1H), 4.00 (br q, *J* = 6.3, 1H), 3.93 (br s, 1H), 3.88−3.80 (om, 2H), 3.63−3.55 (om, 2H), 3.48 (dd, *J* = 9.8, 1.1, 1H), 3.43 (s, 3H), 3.37 (s, 3H), 3.37 (om, 1H), 3.22 (t, *J* = 9.0, 1H), 3.05 (br d, *J* = 2.0, 1H), 2.51 (m, 1H), 2.35−2.16 (om, 5H), 2.02 (m, 1H), 1.92 (dd, *J* = 13.0, 5.0, 1H), 1.81 (br s, 3H), 1.80−1.75 (om, 1H), 1.62−1.41 (om, 5H), 1.49 (s, 3H), 1.24 (od's, J ~ 6.3, 6H), 1.15 (d, *J* = 6.9, 3H), 0.96−0.83 (om, 10H). ^{13}C NMR: δ 173.4, 154.8, 139.3, 138.0, 136.3, 135.2, 133.1, 131.5, 127.8, 124.8, 121.6, 120.4, 118.7, 118.3, 98.7, 95.8, 95.0, 82.0, 80.9, 80.6, 79.4, 77.5, 75.2, 74.9, 73.6, 68.8, 68.5_4, 68.4_9, 68.3_7, 67.3, 66.1, 56.7, 55.3, 50.9, 45.8, 40.5, 39.8, 36.6, 35.2, 34.6, 34.3, 30.6, 29.7, 27.5, 20.2, 19.7, 18.3, 17.3, 16.4, 15.1, 13.0, 12.1. IR (CCl_4) λ_{max}: 3500, 2990, 2930, 1745, 1715, 1450, 1370, 1240, 1160, 1110, 990 cm^{-1}. HRMS: $[M + Li]^+$ = 962.5426 (calcd = 962.5452).

10b. ^1H NMR: δ 5.95 (ddt, *J* = 17.3, 10.6, 5.6, 1H), 5.77−5.61 (om, 5H), 5.52 (dd, *J* = 2.6, 9.9, 1H), 5.40−5.35 (om, 2H), 5.32 (br d, *J* = 5.5, 1H), 5.27 (m, 1H), 5.11−5.01 (om, 2H), 4.80 (br d, *J* = 3.2, 1H), 4.67 (m, 2H), 4.62 (om, 2H), 4.17 (d, *J* = 6.0, 1H), 4.03−3.81 (om, 4H), 3.67−3.56 (om, 2H), 3.46 (br d, *J* = 10.0, 1H), 3.42 (s, 3H), 3.37 (s, 3H), 3.25 (om, 2H), 3.08 (m, 1H), 2.56 (m, 1H), 2.35−2.18 (om, 5H), 1.96−1.76 (om, 3H), 1.80 (s, 3H), 1.70−1.38 (om, 4H), 1.51 (s, 3H), 1.34−1.24 (om, 7H), 1.19 (d, *J* = 7.0, 3H), 0.97−0.82 (om, 10H), 0.15 (s, 9H). ^{13}C NMR: δ 169.9, 155.1, 139.4, 137.2, 136.0, 135.1, 131.5, 130.0, 128.1, 125.0_0, 124.9_7, 121.6, 118.7, 118.6, 98.6, 95.8, 95.1, 84.5, 82.0, 80.4, 79.2, 77.6, 75.1, 74.9, 73.8, 68.7, 68.3, 68.0, 67.8, 67.2, 66.0, 56.5, 55.3, 50.9, 47.1, 40.9, 40.0, 36.3, 35.3, 34.5, 34.2, 30.5, 29.8, 27.5, 20.2, 19.7, 18.3, 17.4, 16.4, 15.1, 13.0, 12.1, 2.1 (3C). IR (CCl_4) λ_{max}: 3400, 2990, 2940, 1740, 1450, 1370, 1305, 1255, 1160, 1110, 990 cm^{-1}. HRMS: $[MH]^+$ = 1028.5784 (calcd = 1028.5766).

4″-*epi*-(Methylamino)-5-*O*-(allyloxycarbonyl)-7-*O*-(trimethylsilyl)-4″-deoxyavermectin B_1 (12). A mixture of ketone **5a** (42.4 g, 44.4 mmol), heptamethyldisilazane (31.9 g, 182 mmol), and $ZnCl_2$ (6.75 g, 49 mmol) in *i*-PrOAc (180 mL) was warmed to 50 °C, aged for 3 h, and then cooled to 5 °C. $NaBH_4$ (8.4 g, 220 mmol) and EtOH (100 mL) were added, while the reaction temperature was maintained at <10 °C, and aged for 1 h at 20 °C. The mixture was treated with 2 N aqueous acetic acid (200 mL) and aged for 15 min. The pH of the mixture was adjusted to 8.0 with 5 N aqueous NaOH, and the precipitated zinc salts were filtered. The aqueous phase was extracted with *i*-PrOAc (3 × 50 mL), and the combined organic phases were evaporated *in vacuo* to give **12** as a yellowish solid (71 g). HPLC assay: isocratic, solvent A:B = 75:25; results: **12** (t_R: B_{1b} = 4.9 min, B_{1a} = 5.8 min, 35.98 g, 34.6 mmol; **13** (t_R: B_{1a} = 6.9 min, 2.68 g, 2.6 mmol; and 4″-*epi*-CH_3NH-7-*O*-TMS-4″-deoxyAVM (t_R: B_{1b} = 2.5 min, B_{1a} = 3.1 min, 2.4 g, 2.5 mmol; assay yield = 83.5% (vs a wt % standard). ^1H NMR: δ 5.95 (ddt, *J* = 17.4, 10.6, 4.8, 1H), 5.77−5.71 (om, 5H), 5.51 (dd, *J* = 9.9, 2.6, 1H), 5.40−5.33 (om, 2H), 5.31 (br d, *J* = 6.0, 1H), 5.26 (m, 1H), 5.11−5.02 (om, 2H), 4.79 (br d, *J* = 3.0, 1H), 4.67 (m, 2H), 4.62 (om, 2H), 4.16 (d, *J* = 6.0, 1H), 3.97−3.80 (om, 4H), 3.80−3.58 (om, 2H), 3.46 (dd, *J* = 9.9, 1.0, 1H), 3.41 (S, 3H), 3.37 (s, 3H), 3.27−3.22 (om, 2H), 2.66 (br d, *J* = 3.3, 1H), 2.57 (s, 3H), 2.56 (om, 1H), 2.32−2.03 (om, 5H), 1.94−1.76 (om, 3H), 1.80 (s, 3H), 1.65−1.33 (om, 4H), 1.50 (s, 3H), 1.32 (om, 1H), 1.26 (d, *J* = 6.4, 3H), 1.24 (d, *J* = 6.0, 3H), 1.18 (d, *J* = 7.0, 3H), 0.96−0.80 (om, 10H), 0.15 (s, 9H). ^{13}C NMR: δ 169.9, 155.1, 139.4, 137.2, 136.0, 135.1, 131.5, 130.0, 128.1, 125.0 (2C), 121.7, 118.7, 118.6, 98.5, 95.8, 95.1, 84.5, 81.9, 80.3, 79.2, 77.6, 75.5, 74.9, 73.8, 68.7, 68.3, 68.0, 67.8, 67.4, 67.2, 60.0, 56.6, 55.5, 47.1, 40.9, 40.0, 38.5, 36.3, 35.3, 34.5, 34.2, 31.1, 30.5, 27.5, 20.2, 19.7, 18.3, 18.2, 16.4, 15.1, 12.9, 12.1, 2.1 (3C). IR (CCl_4) λ_{max}: 3400, 2980, 2940, 1735, 1450, 1375, 1305, 1255, 1165, 1110, 990 cm^{-1}. HRMS: $[MH]^+$ = 1042.5928 (calcd = 1042.5922).

4″-*epi*-Amino-4″-deoxyavermectin B_1 Benzoate (14b). A mixture of crude 4″-*epi*-aminoavermectins **10a,b** (28.4 mmol) and $(Ph_3P)_4Pd(0)$ (33 mg, 0.028 mmol) in EtOH (150 mL) at 5 °C was treated portionwise with $NaBH_4$ (2.15 g, 56.8 mmol). The mixture was aged for 1 h at 5 °C, and then 12 N aqueous HCl (11 mL) was added dropwise to destroy excess borohydride and to acidify (pH = 2.5−3.0) the solution. This mixture was aged for 4 h at 20 °C, diluted with H_2O (200 mL), washed with a mixture of ethyl acetate:hexanes (1:1; 4 × 50 mL), made basic

(15) Poor behavior on a variety of reversed phase columns led us to develop an HPLC assay of the reduction products of the ketone. Prior to workup, the oxidation was assayed for completeness by TLC (Analtech Uniplate, silica gel GF, ethyl acetate:hexanes (1:1); R_f alcohol = 0.35; ketone = 0.65).

with saturated aqueous $NaHCO_3$ (300 mL), and extracted with *i*-PrOAc (4 × 75 mL). The combined extracts were evaporated *in vacuo* to give **14a** as a solid foam weighing 30.1 g. HPLC assay: gradient, solvent, A:B = 40:60–60:40 over 15 min; results: **14a** (B_{1b}: t_R = 6.1 min; 1.7 g, 3.5 mmol; B_{1a}: t_R = 7.4 min; 18.8 g, 21.6 mmol); yield = 88.4%. A sample of crude **14a** (20 g) was filtered through silica gel 60 (20 g), eluting with ethyl acetate to give 11.3 g of purified product. A solution of **14a** (11.3 g, 12.9 mmol) in acetonitrile (45 mL) was treated with benzoic acid (1.72 g, 14.1 mmol) and then aged for 1 h at 20 °C and 1 h at 0 °C to give 4″-*epi*-amino-4″-deoxyavermectin B_1 benzoate (**14b**) (15.1 g) after filtration, washing, and drying *in vacuo* (40 °C, 100 mm Hg), mp = 145.4–148.7 °C.

14b. ^1H NMR: δ 8.08 (m, 2H), 7.53 (m, 1H), 7.43 (m, 2H), 5.87 (m, 1H), 5.76 (dd, *J* = 9.9, 1.5, 1H), 5.74–5.71 (om, 2H), 5.55 (dd, *J* = 9.9, 2.5, 1H), 5.42–5.36 (om, 3H), 5.00 (m, 1H), 4.85 (br s, active H), 4.77 (br d, *J* = 3.0, 1H), 4.68 (m, 2H), 4.30 (br d, *J* = 6.1, 1H), 4.07 (br q, *J* = 6.7, 1H), 3.97 (d, *J* = 6.2, 1H), 3.93 (br s, 1H), 3.90–3.81 (om, 3H), 3.69–3.57 (om, 2H), 3.48 (dd, *J* = 9.8, 1.2, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 3.29 (q, *J* = 2.2, 1H), 3.23 (t, *J* = 9.0, 1H), 2.52 (m, 1H), 2.31–2.20 (om, 4H), 2.04–1.98 (om, 2H), 1.87 (br s, 3H), 1.80–1.73 (m, 2H), 1.64–1.44 (om, 5H), 1.49 (br s, 3H), 1.29 (d, *J* = 6.6, 3H), 1.23 (d, *J* = 6.2, 3H), 1.16 (d, *J* = 6.9, 3H), 1.10 (d, *J* = 6.8, of B_{1b} isomer), 0.96–0.91 (om, 9H), 0.89 (m, 1H). ^{13}C NMR: δ 173.7, 170.6, 139.6, 137.9 (2C), 136.3, 135.1, 132.3, 132.0, 129.8 (2C), 128.1 (2C), 127.7, 124.7, 120.4, 118.3, 118.0, 98.6, 95.8, 95.0, 82.0, 80.8, 80.4, 79.2, 79.1, 74.9, 74.1, 68.38, 68.35, 68.33, 67.7, 67.1, 65.1, 56.6, 55.5, 50.3, 45.7, 40.5, 39.7, 36.6, 35.1, 34.5, 34.2, 30.6, 29.9, 27.5, 20.2, 19.9, 18.2, 17.1, 16.4, 15.1, 12.9, 12.0. IR (CCl_4) λ_{max}: 3560, 3480, 2980, 2940, 1711, 1600, 1530, 1450, 1370, 1160, 1100, 980 cm^{-1}. HRMS: $[M + Li]^+$ = 878.5250 (calcd = 878.5241 for free amine). Anal. Calcd for $C_{55}H_{79}NO_{15}$ (corrected for 0.8 wt % H_2O content): C, 65.91; H, 8.03; N, 1.39. Found: C, 65.88; H, 8.13; N, 1.32.

4″-*epi*-(Methylamino)-4″-deoxyavermectin B_1 Benzoate (1c). A solution of (methylamino)avermectin **12** (8.64 g, 8.29 mmol) and $(Ph_3P)_4Pd(0)$ (5 mg, 0.004 mmol) in EtOH (40 mL) at 5 °C was treated portionwise with $NaBH_4$ (0.62 g, 16.4 mmol). The mixture was aged for 1 h, and then 12 N aqueous HCl (6.5 mL) was added dropwise to destroy the excess borohydride and to acidify (pH = 2.5–3.0) the EtOH solution. This mixture was aged for 4 h at 20 °C, diluted with H_2O (75 mL), washed with a mixture of ethyl acetate:hexanes (1:1; 4 × 50 mL), made basic with saturated aqueous $NaHCO_3$ (125 mL), and extracted with *i*-PrOAc (4 × 50 mL). The combined extracts were evaporated *in vacuo* to give **1a** as a solid foam (10.1 g). HPLC assay: gradient, solvent A:B = 50:50–85:15 over 20 min; results: **1a** (B_{1b}: t_R = 4.4 min, 0.56 g, 0.6 mmol; B_{1a}: t_R = 5.64 min, 5.44 g, 6.1 mmol); assay yield = 81.6% (vs a wt % standard). A solution of **1a** (5.56 g, 6.2 mmol by assay) in MTBE (20 mL) was treated with benzoic acid (0.76 g, 6.2 mmol) and then hexanes (40 mL) was added. After aging at 25 °C for 1 h, the mixture was cooled to 2 °C, aged 2 h, then filtered. The crystals were washed with 50 v % MTBE in hexanes (50 mL) and dried *in vacuo* to give 5.7 g of **1c**, mp (DSC at 10 °C/min) = 137–144 °C.

1c. ^1H NMR: δ 8.10 (m, 2H), 7.53 (m, 1H), 7.43 (m, 2H), 5.87 (m, 1H), 5.76 (dd, *J* = 9.8, 1.7, 1H), 5.75–5.72 (om, 2H), 5.55 (dd, *J* = 9.8, 2.6, 1H), 5.43–5.37 (om, 3H), 5.22 (v br, active H), 5.00 (m, 1H), 4.76 (br d, *J* = 3.0, 1H), 4.69 (m, 2H), 4.30 (br d, *J* = 6.1, 1H), 4.03 (br q, *J* = 6.7, 1H), 3.98 (d, *J* = 6.2, 1H), 3.94 (br s, 1H), 3.88 (m, 2H), 3.82 (dq, *J* = 9.1, 6.2, 1H), 3.74 (ddd, *J* = 11.5, 5.0, 3.8, 1H), 3.58 (m, 1H), 3.48 (dd, *J* = 9.9, 1.3, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 3.30 (q, *J* = 2.2, 1H), 3.23 (dd, *J* = 9.1, 8.7, 1H), 2.87 (br d, *J* = 3.8, 1H), 2.67 (s, 3H), 2.52 (m, 1H), 2.31–2.25 (om, 3H), 2.21 (dd, *J* = 12.7, 5.0, 1H), 2.05–1.90 (om, 2H), 1.87 (br s, 3H), 1.78 (m, 1H), 1.63–1.46 (om, 6H), 1.49 (br s, 3H), 1.34 (d, *J* = 6.7, 3H), 1.23 (d, *J* = 6.2, 3H), 1.16 (d, *J* = 7.0, 3H), 1.11 (d, *J* = 7.1, of B_{1b} isomer), 0.96–0.91 (om, 9H), 0.89 (m, 1H). ^{13}C NMR: δ 173.7, 170.9, 139.6, 138.0, 137.9, 136.3, 135.1, 132.2, 132.1, 129.9 (2C), 128.1 (2C), 127.7, 124.7, 120.4, 118.3, 118.0, 98.5, 95.7, 95.0, 81.9, 80.8, 80.4, 79.2, 79.1, 74.9, 74.8, 68.4_2, 68.3_6, 68.3_3, 67.7, 67.2, 66.6, 59.9, 56.6, 55.6, 45.7, 40.5, 39.7, 37.1, 36.6, 35.1, 34.5, 34.2, 30.9, 30.6, 27.5, 20.1, 19.9, 18.2, 17.9, 16.4, 15.1, 12.9, 12.0. IR (CCl_4) λ_{max}: 3595, 3460, 2995, 2940, 1715, 1455, 1380, 1160, 1120, 990 cm^{-1}. HRMS: $[MH]^+$ = 886.5316 (calcd = 886.5316) for free amine. Anal. Calcd for $C_{56}H_{81}NO_{15}$: C, 66.71; H, 8.10; N, 1.39. Found: C, 66.96; H, 7.82; N, 1.45.

4″-*epi*-(Acetylamino)-4″-deoxyavermectin B_1 (2). A solution of aminoavermectin **14a** (9.24 g, 10.6 mmol by assay) in *i*-PrOAc (45 mL) was cooled to 5 °C and acetic anhydride (1.4 g, 13.8 mmol) was added over 5 min. The mixture was aged for 1 h and then poured into saturated aqueous $NaHCO_3$ (25 mL). The *i*-PrOAc layer was concentrated *in vacuo* to a yellowish solid (14.4 g) which was then dissolved into acetonitrile (35 mL) at reflux under N_2 and crystallized by slow cooling to 2 °C over a 2 h period. The slurry was aged for 1 h and then filtered. The product was washed with cold (2 °C) acetonitrile (20 mL). The resulting cake was dried *in vacuo* at 50 °C to give 8.00 g (82% yield) of amide **2** as a crystalline solid, mp = 163.3–165.7 °C. HPLC assay: gradient, solvent A:B = 45:55–65:35 over 15 min; results: **2** (B_{1b}: t_R = 8.8 min; B_{1a}: t_R = 10.8 min). ^1H NMR: δ 5.86 (m, 1H), 5.84–5.70 (om, 3H), 5.59 (d, *J* = 10.0, 1H), 5.55 (dd, *J* = 9.9, 2.5, 1H), 5.43–5.38 (om, 3H), 4.98 (m, 1H), 4.77 (d, *J* = 3.2, 1H), 4.73–4.65 (m, 2H), 4.44 (dd, *J* = 10.0, 3.2, 1H), 4.30 (br t, J ~ 5, 1H), 4.06 (dq, *J* = 6.6, 3.2, 1H), 4.03 (s, OH), 3.97 (d, *J* = 6.3, 1H), 3.93 (br s, 1H), 3.87–3.82 (om, 2H), 3.71–3.58 (om, 2H), 3.49 (dd, *J* = 10.0, 1.3, 1H), 3.44 (s, 3H), 3.40 (s, 3H), 3.30 (q, *J* = 2.2, 1H), 3.21 (t, *J* = 9.0, 1H), 2.52 (m, 1H), 2.39 (br d, J ~ 7, OH), 2.31–2.21 (om, 4H), 2.07 (s, 3H), 2.05–2.00 (om, 2H), 1.87 (br s, 3H), 1.77 (m, 1H), 1.64–1.45 (om, 6H), 1.49 (br s, 3H), 1.24 (d, *J* = 6.2, 3H), 1.16 (d, *J* = 6.9, 3H), 1.13 (d, *J* = 6.6, 3H), 0.98–0.90 (om, 9H), 0.89 (m, 1H). ^{13}C NMR: δ 173.8, 170.7, 139.7, 138.0_2, 137.9_7, 136.3, 135.1, 127.7, 124.8, 120.4, 118.3, 118.0, 98.7, 95.8, 95.0, 82.0, 81.1, 80.4, 79.3, 79.1, 74.9, 73.3, 68.5, 68.4 (2C), 67.7, 67.1, 65.5, 56.7, 56.1, 48.4, 45.7, 40.5, 39.8, 36.7, 35.2, 34.5, 34.3, 31.9, 30.6, 27.5, 23.6, 20.3, 20.0, 18.3, 17.1, 16.4, 15.2, 13.0, 12.1. IR (CCl_4) λ_{max}: 3590, 3480, 2990, 2940, 1712, 1685, 1510, 1450, 1380, 1150, 1130, 990 cm^{-1}. HRMS: $[M + Li]^+$ = 920.5349 (calcd = 920.5347). Anal. Calcd for $C_{50}H_{75}NO_{14}$: C, 65.70; H, 8.27; N, 1.52. Found: C, 65.79; H, 7.96; N, 1.46.

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Supplementary Material Available: ^1H NMR spectra for compounds **4**, **5a**, **10a**, **10b**, and **12** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.