Practical Syntheses of 13-*O*-[(2-Methoxyethoxy)methyl]-22,23-dihydroavermectin B_1 Aglycon [Dimedectin Isopropanol, MK-324] and 13-*epi*-*O*-(Methoxymethyl)-22,23-dihydroavermectin B_1 Aglycon [L-694,554], Flea Active Ivermectin Analogues

Raymond J. Cvetovich,* Chris H. Senanayake,† Joseph S. Amato, Lisa M. DiMichele, Timothy J. Bill, Robert D. Larsen, R. F. Shuman, Thomas R. Verhoeven, and Edward J. J. Grabowski

Department of Process Research, Merck Research Laboratories, Division of Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065

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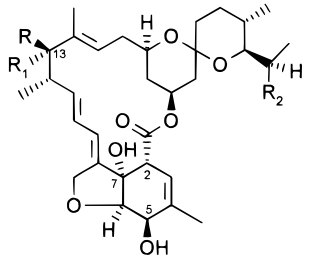
Practical high yielding syntheses of 13-*O*-[(2-methoxyethoxy)methyl]-22,23-dihydroavermectin B_1 aglycon (dimedectin 2-propanol, MK-324, **1**) and 13-*epi*-*O*-(methoxymethyl)-22,23-dihydroavermectin B_1 aglycon (L-694,554, **2**), both potent flea insecticides, from ivermectin are presented. The successful selective manipulation of silyl protecting groups on ivermectin aglycon led to the facile preparation of 5,7-*O*-bis-silyl-22,23-dihydroavermectin B_1 aglycon **7** as the key intermediate for the large scale syntheses of these compounds. Development of a dual pyridine/tertiary amine system for mesylation of the C-13α hydroxyl group of **7** and subsequent displacement with cesium propionate−propionic acid led to the successful inversion of the 13-hydroxy group.

The avermectins[1a] and the related milbemycins,[1b] 16-membered macrolides produced by *Streptomyces avermitilis* or *Streptomyces hygroscopicus*, respectively, are potent anthelmintic and insecticidal compounds used in agriculture, animals, and man. Some of the commercialized successes of this class of compounds are: Agrimec, Ivomec, Doramectin, Interceptor, Cydectin, and Milbeknock. Among the many efforts to improve the biological profile and reduce toxicity in animals and humans of avermectins, analogues modified at the C-13 position were prepared.[2] In addition, C-13 *epi*-avermectin analogues were investigated in the search for improved safety margins.[3] Among the structural variations examined, those exhibiting interesting insecticidal activity are 13-*O*-[(2-methoxyethoxy)methyl]-22,23-dihydroavermectin B_1 aglycon (MK-324, **1**)[2] and 13-*epi*-*O*-(methoxymethyl)-22,23-dihydroavermectin B_1 aglycon (L-694,554, **2**, Figure 1) which are active agents for the control of flea infestations in dogs.



B_{1a}, $R_2 = CH_2CH_3$ (≥90%)
B_{1b}, $R_2 = CH_3$ (≤10%)

1: MK-324 R = H, R_1 = OMEM
2: L-694,554 R = OMOM, R_1 = H

Figure 1. MK-324, **1**, and L-694,554, **2**.

Results and Discussion

Published procedures on the preparation of MK-324[2] relied on (2-methoxyethoxy)methyl (MEM) derivatization of the monoprotected 5-*O*-*tert*-butyldimethylsilyl(TBDMS)-22,23-dihydroavermectin B_1 aglycon **4**. This approach gave rise to the formation of significant amounts of bis-MEM derivative **5**, requiring conventional preparative silica gel column chromatography to remove this undesirable byproduct. Attempts were made to selectively hydrolyze bis- and tris-MEM substituted intermediates but failed to produce significant yields of mono-MEM **1**. A selective silylation and desilylation of ivermectin aglycon was developed to prepare a 5,7-*O*-bis-protected aglycon intermediate, which allowed the preparation of large quantities of MK-324 and L-694,554.

The aglycon of 22,23-dihydroavermectin B_1 (**3**), (see Figure 2, only B_{1a} isomer shown) was prepared by acid-catalyzed solvolysis of ivermectin.[4] This hydrolysis was complicated by the susceptibility of the aglycon toward acid catalyzed Grob-like fragmentation to produce ring-opened aldehydes.[5] Hydrolysis was best accomplished in 5% H_2SO_4 in methanol at temperatures below 30 °C, producing aglycon **3** in 93% yield. Silylation of aglycon **3** with excess TBDMSCl/imidazole in THF at 55 °C produced monoprotected aglycon **4**, exclusively. The addition of excess TMSCl/imidazole to monoprotected **4** trimethylsilylated the remaining C-7 and C-13 hydroxy groups to produce tris-protected aglycon **6** in >95%

† Current address: Sepracor Inc., Department of Pharmaceuticals, 111 Locke Dr., Marlborough, MA 01752.

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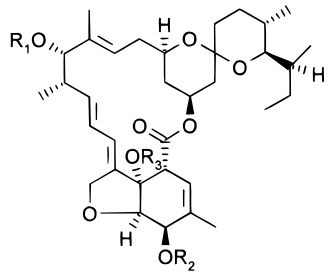

3: $R_1 = R_2 = R_3 = H$
4: $R_1 = R_3 = H$, R_2 = TBDMS
5: $R_1 = R_3$ =MEM, R_2 = TBDMS
6: $R_1 = R_3$ = TMS, R_2 = TBDMS
7: R_1 = H, R_2 = TBDMS, R_3 = TMS
8: R_1 = MEM, R_2 = TBDMS, R_3 = TMS
9: $R_1 = SO_2CH_3$, R_2 = TBDMS, R_3 = TMS

Figure 2. Ivermectin aglycon intermediates.

yield. The combination of these silylation steps was easily bundled into a one-pot procedure to provide tris-silyl-protected **6** in 95% overall yield.

The more difficult task of selective removal of either the C-7 or C-13 TMS group was then tackled. A variety of acid, solvent, nucleophile, and temperature parameters were investigated, most of which failed to selectively remove the less sterically hindered C-13 *O*-TMS group. A selective mono-deprotection of the C-13 hydroxyl group was effected using dichloroacetic acid in 13% aqueous THF at 20 °C, which left the C-7 *O*-TMS and C-5 *O*-TBDMS groups intact affording 5-*O*-TBDMS-7-*O*-TMS-22,23-dihydroavermectin B_1 aglycon, **7**, in 93% yield. Alkylation of **7** with MEM-Cl and diisopropylethylamine (DIPEA) was achieved in acetonitrile from which the resulting MEM-ether **8** was directly crystallized in 86% yield. The rate of alkylation was found to be highly sensitive to the amount of DIPEA used in the reaction. An excess of base slowed the alkylation rate. It was also found that samples of MEM-Cl that contained HCl due to decomposition led to slower rates of alkylation. In fact, the addition of excess DIPEA·HCl to reactions induced slower rates of alkylation.

A mild removal of the TMS and TBDMS protecting groups in the presence of the MEM group of derivative **8** was accomplished with HCl in methanol at 50 °C. Following the deprotection, MK-324 (**1**) was crystallized from ethanol/water, producing an ethanol solvate which proved to be unstable to long term storage. Among the multiple degradates isolated were the 22,23-dihydroavermectin B_1 aglycon, **3**, and a ring-opened aldehyde.[4] Single crystal X-ray analysis of the ethanolate revealed that the position of the ethanol in the crystal adjacent to the MEM group predisposed this group to solvolysis within the crystal structure. MK-324 (**1**) was crystallized from 2-propanol/water to produce a 2-propanol solvate. Single crystal X-ray analysis of this solvate indicated it shared the same positioning within the crystal packing as the ethanolate, but this solvate has proved to be stable to ambient storage.

Procedures for the preparation of inverted 13β-avermectin and 13β-*O*-milbemycin analogues have been published, including (1) solvolysis of C-13β iodo intermediates,[3,6] (2) epoxidation, ring opening, and rearrangement of milbemycin,[7] microbiological hydroxylation,[8] selenium dioxide allylic oxidation,[9] and inversion−displacement of a tosylate with tetrabutylammonium nitrate.[10]

While the preparation of the C-13α *O*-tosyl of ivermectin B_1 aglycon with *p*-toluenesulfonic anhydride, displacement with nitrate, and reductive removal of the nitrate ester with Zn/HOAc (50% yield overall) represented a significant accomplishment in the preparation of C-13β *O*-derivatives, problems remained that were essential to overcome in order to develop an attractive process for the preparation of L-694,554, **2**. Alternate chemistry[11] was explored toward the accomplishment of the transformation.

When bis-silyl-protected ivermectin aglycon **7** was treated with methanesulfonyl chloride/triethylamine, a complex mixture of products was produced with a low yield of mesylate **9**. The use of diisopropylethylamine as base resulted in an increase in the yield of mesylate **9** to 65%, while the use of bases with the p*K* in the range of 5.5−7, such as pyridine, lutidine, (dimethylamino)pyridine, or collidine, afforded low yields. However, the coaddition of a pyridine base ((dimethylamino)pyridine, collidine, or 2,6-lutidine) with a tertiary alkylamine base resulted in significant enhancement of the mesylate formation. A highly effective procedure for the mesylation of alcohol **7** was developed using methanesulfonyl chloride (2 equiv) in the presence of diisopropylethylamine (3 equiv) and (dimethylamino)pyridine (2 equiv) in dichloromethane at −10 °C, which resulted in the formation of mesylate **9** (Figure 2) in >95% isolated yield. The mesylation is believed to proceed through the intermediacy of pyridinium sulfonyl ions and to not involve formation of sulfenes as the mesylating reagent, with the more basic tertiary amines serving to deprotonate and activate the alcohol (based on NMR studies). The isolation of mesylate **9** required the avoidance of an acidic workup due to the presence of the acid-labile silyloxy protecting groups, and this was accomplished by precipitation of the trialkylammonium and pyridinium salts with hexanes, followed by an aqueous bicarbonate wash.

The inversion/displacement of mesylate **9** was explored, utilizing an array of reagents. Tetrabutylammonium nitrate or Amberlyst A-26 nitrate (prepared from amberlyst A-26 chloride) requires long reaction times at 40−50 °C in toluene to produce 50−58% yields of nitrate ester **10** (see Figure 3, only B_{1a} isomer shown). Potassium nitrate in DMSO produced mixtures of nitrate ester **10** and nitro derivative **11**. Potassium formate, tetrabutylammonium formate, and potassium superoxide/18-crown-6 displacements led to complex mixtures of byproducts, some involving epimerization at C-2, migration of the C-3,4 double bond, and subsequent aromatization due to the base sensitivity of the avermectins.[12] Cesium acetate/18-crown-6 produced a 50% yield of acetate **12**, along with

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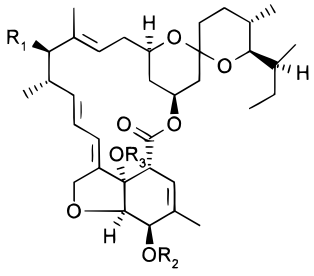

10: $R_1 = ONO_2$, R_2 = TBDMS, R_3 = TMS
11: $R_1 = NO_2$, R_2 = TBDMS, R_3 = TMS
12: $R_1 = OCOCH_3$, R_2 = TBDMS, R_3 = TMS
13: $R_1 = OCOCH_2CH_3$, R_2 = TBDMS, R_3 = TMS
14: $R_1 = OCOCH_2CH_3$, R_2 = TBDMS, R_3 = H
15: R_1 = OH, R_2 = TBDMS, R_3 = TMS
16: R_1 = OMOM, R_2 = TBDMS, R_3 = TMS

Figure 3. Inverted C-13 intermediates.

base-derived decomposition (~25%). Capitalizing on the positive effect of cesium[13] and attempting to buffer the basicity of the reagent, we treated cesium acetate with an equimolar amount of acetic acid, which resulted in control of the base-catalyzed decomposition (<5%). Due to the hygroscopicity of cesium acetate, cesium propionate/propionic acid was utilized for further development. Hydrolytic workup resulted in a 10−20% loss of the C-7 *O*-TMS group to give C-7 alcohol **14**. Consequently, crude product was treated with TMS-Cl/imidazole to give propionate **13** in a 68% yield from mesylate **9**. The sensitivity of the C-7 *O*-TMS group required that mild propionate hydrolysis conditions be developed. Smooth transesterification conditions using titanium tetraisopropoxide[14] in 2-propanol were found, and, with the workup modified using 2% aqueous H_3PO_4, inverted alcohol **15** was isolated in 90% yield as a crystalline solid. This route afforded inverted alcohol **15** in 60% yield from alcohol **7**.

Preparation of the MOM-derivative of alcohol **15** utilized MOM-Cl prepared via the procedure of Amato et al.[15] This alkylation gave MOM-intermediate **16** in 98% yield. Use of commercially available MOM-Cl led to formation of minor amounts of chloro-analogues (due to the presence of bis-(chloromethoxymethyl) ether) which were difficult to remove from the product without extensive chromatography. Removal of the silyl-based protecting groups in the presence of the MOM-group, as in the case of selective deprotection of MEM-intermediate **8**, was achieved using 1% HCl in methanol at 25 °C with stirring for 2.5 h. This mild deprotection produced L-694,554, **2**, in 98% yield.

The selective manipulation of protecting groups on ivermectin aglycon produced intermediate bis-silyl ivermectin aglycon **7**, which was derivatized and converted to MK-324. In addition, bis-silyl ivermectin aglycon **7** was successfully inverted via its mesylate, using cesium propionate/propionic acid to produce propionate **13**, which was hydrolyzed via Ti(O-*i*-Pr)$_4$-catalyzed transesterification. Preparation of the *O*-MOM derivative and selective desilylation successfully yielded L-694,554. Both agents have exhibited antiflea activity on dogs and are being evaluated for their commercial opportunities.

Experimental Section

General. HPLC analyses were performed using a Spectra-Physics SP8700 ternary solvent delivery system, a Vydac C18 protein/peptide column (250 × 4.6 mm, 5 μm) reverse phase column, solvent system A:B, acetonitrile:water (with 0.1 v % H_3PO_4), at 25 °C, 3.0 mL/min, with UV detection at 245 nm. Samples of each product for characterization and use as HLPC standards were isolated and purified by column chromatography (E. Merck Silica Gel 60, 230−400 mesh ASTM) using ethyl acetate:hexanes mixtures. All reactions were carried out under an atmosphere of N_2, and solvents and reagents were dried only where needed over 3 Å or 4 Å molecular sieves prior to use. 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. High resolution mass spectroscopy studies were performed in the FAB mode. 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.

22,23-Dihydro-5-*O*-TBDMS-7,13-*O*-bis-TMS-avermectin B_1 Aglycon (6). A solution of 22,23-dihydroavermectin B_1 aglycon **3**[4] (55.6 g, 0.095 mol) in THF (600 mL) was treated with imidazole (27.7 g, 0.39 mol) and *tert*-butyldimethylsilyl chloride (26.3 g, 0.175 mol). The mixture was heated to 55 °C and stirred for 4 h. The reaction mixture was cooled to 10 °C, and additional imidazole (43.6 g, 0.64 mol) and trimethylsilyl chloride (41.4 mL, 0.325 mol) were added. The mixture was stirred for 15 h at 20−25 °C, cooled to 5 °C, and then diluted with hexanes (750 mL). The mixture was washed with cold 5% aqueous H_3PO_4, saturated aqueous $NaHCO_3$, and then water. The organic phase was concentrated *in vacuo* and dissolved with THF to give 77.6 g (95.5% yield) of **6** by HPLC analysis. ^{1}H NMR: δ 5.79−5.61 (om, 3H), 5.47 (br s, 1H), 5.35 (m, 1H), 4.80 (m, 1H), 4.66 (dd, J = 14.1, 2.0, 1H), 4.55 (dd, J = 14.1, 2.0, 1H), 4.39 (m, 1H), 3.94 (br s, 1H), 3.80 (d, J = 5.2, 1H), 3.67 (m, 1H), 3.22 (m, 2H), 2.51 (m, 1H), 2.36 (dd, J = 10.7, 3.4, 1H), 2.32−2.22 (om, 2H), 1.82 (m, 1H), 1.78 (s, 3H), 1.65−1.32 (om, 9H), 1.50 (s, 3H), 1.16 (t, J = 11.4, 1H), 1.08 (d, J = 6.9, 3H), 0.97−0.77 (om, 18H), 0.13 (s, 24H). ^{13}C NMR: δ 170.7, 139.7, 138.1, 137.3, 134.2, 124.4, 121.1, 120.5, 118.4, 97.5, 83.5, 80.7, 78.6, 76.6, 69.5, 69.1, 67.5$_0$, 67.4$_4$, 47.3, 41.9, 40.3, 36.4, 35.7, 35.6, 34.2, 31.3, 28.2, 27.2, 25.9 (3C), 20.0, 19.9, 18.4, 17.5, 14.6, 12.4, 12.0, 2.4 (3C), 0.12 (3C), −4.4$_6$, −4.6$_6$.

5-*O*-TBDMS-7-*O*-TMS-22,23-Dihydroavermectin B_1 Aglycon (7). A solution of 5-*O*-TBDMS-7,13-*O*-bis-TMS-22,23-dihydroavermectin B_1 aglycon (**6**, 77.6 g, 0.0918 mol) in THF (700 mL) was treated with water (104 mL) and dichloroacetic acid (4.5 mL, 0.055 mol) and stirred at 20−25 °C for 48 h. The reaction was poured into saturated aqueous $NaHCO_3$ (650 mL) and extracted with MTBE (650 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (650 mL) and with saturated aqueous NaCl (250 mL). The organic phase was azeotropically dried, concentrated, and then diluted with acetonitrile to give 66.0 g (92.6% yield) of **7** by HPLC analysis. ^{1}H NMR: δ 5.81 (m, 1H), 5.46 (m, 2H), 5.48−5.40 (om, 2H), 4.81 (m, 1H), 4.67 (dd, J = 14.2, 2.1, 1H), 4.55 (dd, J = 14.2, 2.1, 1H), 4.39 (br s, 1H), 3.80 (d, J = 5.2, 1H), 3.70 (m, 1H), 3.22 (br s, 1H), 3.18 (br d, J = 7.5, 1H), 2.58 (m, 1H), 2.40−2.23 (om, 3H), 1.83 (m, 1H), 1.78 (s, 2H), 1.70 (d, J = 3.3, 1H), 1.65−1.58 (om, 2H), 1.55 (s, 3H), 1.55−1.44 (om, 5H), 1.38 (m, 2H), 1.27 (m, 1H), 1.20 (d, J = 7.0, 3H), 1.16 (t, J = 11.5, 1H), 1.03−0.83 (om, 16H), 0.79 (d, J = 5.4, 3H), 0.13, (s, 6H), 0.11 (s, 9H). ^{13}C NMR: δ 170.6, 140.1, 138.7, 136.0, 134.2, 124.9, 121.1, 120.3, 117.6, 97.5, 83.4, 80.8, 77.6, 77.3, 68.5, 69.0, 67.4$_0$, 67.3$_4$, 47.4, 41.9, 39.6, 36.4, 35.7, 35.6, 34.3, 31.3, 28.1, 27.5, 25.9 (3C), 20.0, 19.3, 18.4, 17.5, 14.6, 12.5, 11.6, 2.3 (3C), −4.4$_6$, −4.6$_6$.

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13-*O*-MEM-5-*O*-TBDMS-7-*O*-TMS-22,23-Dihydroavermectin B_1 Aglycon (8). To a solution of 5-*O*-TBDMS-7-*O*-TMS-22,23-dihydroavermectin B_1 aglycon (**7**, 66.0 g, 0.085 mol) in acetonitrile (400 mL) were added DIPEA (82.3 mL, 0.472 mol) and MEM chloride (51.2 mL, 0.44 mol). The solution was warmed to 55−60 °C and aged for 4 h. The mixture was cooled to 5 °C, and water (20 mL) was added dropwise over 10 min. The solution was seeded and aged for 20 h at 0 °C. The crystals were filtered, washed with cold acetonitrile, and dried with a stream of nitrogen to give 63 g of **8** as a white solid, mp 152−155 °C. ^{1}H NMR: δ 5.78 (dd, J = 14.9, 11.0, 1H), 5.71−5.61 (om, 2H), 5.46 (br s, 1H), 5.28 (m, 1H), 4.81 (m, 1H), 4.77 (d, J = 7.0, 1H), 4.70 (d, J = 7.0, 1H), 4.67 (dd, J = 14.3, 2.0, 1H), 4.54 (dd, J = 14.3, 2.0, 1H), 4.39 (br s, 1H), 4.00 (br s, 1H), 3.65 (dt, J = 11.2, 4.5, 2H), 3.79 (d, J = 5.2, 1H), 3.73−3.62 (om, 2H), 3.56 (t, J = 4.7, 2H), 3.39 (s, 3H), 3.21 (m, 1H), 3.17 (br d, J = 7.6, 1H), 2.61 (m, 1H), 2.38−2.23 (om, 3H), 1.83 (m, 1H), 1.78 (s, 3H), 1.64-1.43 (om, 7H), 1.52 (s, 3H), 1.38 (m, 2H), 1.18 (d, J = 6.9, 3H), 1.03−0.76 (om, 18H), 0.13_4 (s, 3H), 0.12_9 (s, 3H), 0.11 (s, 9H). ^{13}C NMR: δ 170.6, 140.2, 136.7, 135.1, 134.1, 124.9, 121.0, 120.3, 118.6, 97.5, 94.5, 83.4, 82.6, 80.7, 77.3, 71.8, 69.4, 68.9, 67.7, 67.3 (2C), 59.1, 47.3, 41.9, 39.4, 36.5, 35.6_5, 35.5_9, 34.3, 31.2, 28.1, 27.5, 25.9 (3C), 20.0, 19.8, 18.4, 17.4, 14.8, 12.4, 11.5, 2.3 (3C), −4.5, −4.7. Anal. Calcd for $C_{47}H_{80}O_{10}Si_2$: C, 65.54 ; H, 9.36. Found: C, 65.14; H, 9.36.

13-*O*-MEM-22,23-Dihydroavermectin B_1 Aglycon (1). A solution of 13-*O*-MEM-5-*O*-TBDMS-7-*O*-TMS-22,23-dihydroavermectin B_1 aglycon (**8**, 63.0 g, 0.073 mol) in methanol (600 mL) at 50 °C was treated with a solution of HCl in methanol (1.55 mL of 12 N HCl in 100 mL methanol). After complete addition, the mixture was cooled to 20 °C and aged for 14 h. MTBE (80 mL) and 4% aqueous $NaHCO_3$ (1.6 L) were added and the phases separated. The aqueous phase was extracted with MTBE (80 mL), and the combined organic phases were washed with water (100 mL). The solvent was evaporated, and the residue was dissolved into acetonitrile (400 mL) and washed with heptane (5 × 80 mL). The acetonitrile was evaporated *in vacuo*, and the residue was dissolved into *i*-PrOH (400 mL). The solution was warmed to 50 °C, water was added (240 mL), and the mixture was seeded. The crystalline mixture was cooled to 0 °C over 6 h, aged for 18 h, and filtered and washed with 1:1 *i*-PrOH:water. The crystalline cake was dried *in vacuo* at 25 °C to give 44.6 g of **1** as a crystalline white solid, mp 103.5−105 °C, containing 8.2 wt % *i*-PrOH (GC assay). ^{1}H NMR: δ 5.82 (m, 1H), 5.70 (om, 2H), 5.41 (br s, 1H), 5.30 (m, 1H), 5.17 (br d, J = 11.1, 1H), 4.71−4.62 (om, 4H), 4.28 (m, 1H), 4.09 (s, active H), 3.95−3.94 (om, 2H), 3.90 (m, 1H), 3.71−3.62 (om, 2H), 3.55 (m, 2H), 3.39 (s, 3H), 3.25 (q, J = 2.3, 1H), 3.19 (dd, J = 9.0, 1.4, 1H), 3.09 (dd, J = 9.5, 2.0, 1H, B_{1b} component), 2.53 (m, 1H), 2.39 (d, J = 8.2, active H), 2.28 (om, 2H), 1.97 (ddd, J = 11.8, 4.8, 1.3, 1H), 1.86 (s, 3H), 1.75 (dm, J = 12.5, 1H), 1.65 (m, 1H), 1.58−1.38 (om, 7H), 1.50 (s, 3H), 1.32 (t, J = 11.8, 1H), 1.14 (d, J = 6.9, 3H), 1.05 (d, J = 6.9, 3H, B_{1b} component), 0.95 (t, J = 7.3, 3H), 0.85 (d, J = 6.8, 3H), 0.85−0.75 (om, 4H). ^{13}C NMR: δ 173.6, 139.7, 138.0, 137.8, 135.1, 124.7, 120.4, 118.3, 97.4, 94.4, 82.6, 80.3, 79.1, 77.3, 71.8, 68.6, 68.5, 67.8, 67.6, 67.3, 59.1, 45.7, 41.3, 39.9, 36.9, 35.8, 35.6, 34.3, 31.3, 28.1, 27.5, 25.4, 20.0, 19.6, 17.5, 14.9, 12.5, 11.8. Anal. Calcd for $C_{41}H_{66}O_{10}$ (2-propanol solvate): C, 67.00; H, 9.05. Found: C, 66.83; H, 8.96.

13α-*O*-Mesyl-5-*O*-TBDMS-7-*O*-TMS-22,23-dihydroavermectin B_1 Aglycon (9). A solution of crude alcohol **7** (31.3 g, 0.040 mol), (dimethylamino)pyridine (9.76 g, 0.08 mol), and diisopropylethylamine (20.9 mL, 0.12 mol) in dichloromethane (125 mL) was cooled to −5 °C. Methanesulfonyl chloride (9.5 mL, 0.12 mol) was added, and the mixture was stirred at 0 °C for 45 min. Hexanes (0.46 L) were added, the reaction mixture was filtered through a silica-gel pad (15 g, 230−400 mesh), and the cake was washed with hexanes (230 mL). The combined filtrates were mixed with 5% aqueous $NaHCO_3$ (460 mL) and ethyl acetate (230 mL). The organic layer was washed with 5% aqueous NaCl (460 mL), dried over sodium sulfate (50 g), filtered, and concentrated *in vacuo* to afford 45 g of mesylate **9** as a yellow solid in 92% yield (69 wt % assay by HPLC). HPLC: gradient elution, A:B, 90:10 to 100:0 in 30 min, t_R(min) 13α-alcohol **7**, B_{1b}, B_{1a} 5.75, 6.43 min; 13α-mesylate **9**, B_{1b}, B_{1a} 4.50, 5.16 min. ^{1}H NMR: δ 5.85 (dd, J = 15.0, 11.3, 1H), 5.70 (dt, J = 11.3, 2.2, 1H), 5.59 (dd, J = 15.0, 9.7, 1H), 5.51−5.47 (om, 2H), 4.95 (br s, 1H), 4.84 (m, 1H), 4.68 (dd, J = 14.3, 2.3, 1H), 4.56 (dd, J = 14.3, 2.1, 1H), 4.40 (m, 1H), 3.81 (d, J = 5.2, 1H), 3.71 (m, 1H), 3.23 (q, J = 2.3, 1H), 3.17 (m, 1H), 3.03 (s, 3H), 2.74 (m, 1H), 2.36−2.25 (om, 3H), 1.79 (s, 3H), 1.77 (om, 1H), 1.63−1.37 (om, 6H), 1.62 (s, 3H), 1.41 (m, 2H), 1.24 (d, J = 7.0, 3H), 1.16 (t, J = 11.5, 1H), 0.98−0.83 (om, 4H), 0.94 (s, 9H), 0.87 (d, J = 6.7, 3H), 0.79 (m, 3H), 0.15 (s, 3H), 0.14 (s, 12H). ^{13}C NMR: δ 170.5, 141.6, 134.3, 134.2, 133.3, 126.0, 120.7, 120.5, 120.3, 95.6, 87.8, 83.4, 80.7, 77.5, 69.4, 68.7, 67.3, 67.0, 47.3, 41.8, 39.4, 38.9, 36.5, 35.7, 35.6, 34.4, 31.2, 28.1, 27.5, 25.9 (3C), 20.0, 19.4, 18.4, 17.5, 14.7, 12.5, 11.6, 2.4 (3C), -4.5, −4.7. HRMS: $[M + H]^+$ = 851.3054 (calculated = 851.4619).

13β-*O*-Propionyl-5-*O*-TBDMS-7-*O*-TMS-22,23-dihydroavermectin B_1 Aglycon (13). A mixture of cesium carbonate (3.53 g, 10.0 mmol), 18-crown-6 (3.8 g, 11.7 mmol), toluene (240 mL), and propionic acid (3.0 mL, 40.0 mmol) was heated at 110 °C for 2 h. Mesylate **9** (10 g, 11.7 mmol) in toluene (30 mL) was added, and the reaction mixture was heated at 110 °C for 2.5 h. The mixture was then cooled to 10 °C, hexanes (500 mL) were added, the mixture was filtered, and the filtrate was diluted with ethyl acetate (250 mL). The solution was washed with 5% aqueous $NaHCO_3$ (300 mL) and saturated aqueous NaCl (300 mL) and then dried over magnesium sulfate (20 g), filtered, and concentrated *in vacuo* to afford 9.3 g of crude 13β-propionate **13**. Due to partial desilylation, the crude propionate and imidazole (5.69 g, 89 mmol) were dissolved in THF (140 mL), and the solution was cooled to 0 °C. Chlorotrimethylsilane (5.34 mL, 42 mmol) was added, and the mixture was stirred at 0 °C for 10 min. The reaction mixture was then allowed to warm to room temperature and stirred for 19 h. Hexanes (300 mL) were added, and the mixture was filtered. The filtrate was washed with 5% aqueous $NaHCO_3$ (300 mL) and saturated aqueous NaCl (300 mL), dried over sodium sulfate (50 g), filtered, and concentrated *in vacuo* to afford 9.4 g of crude 13β-propionoate **13**. The crude product was chromatographed on silica gel (250 g, hexanes:ethyl acetate, 95:5) to afford 6.67 g of off-white solid of 13-β-propionate **13** in 68% yield with a purity of >96 area % by HPLC. HPLC: gradient elution, A:B, t_R(min) 13α-mesylate, **9** B_{1b}, B_{1a} 4.47, 5.16; 13β-propionate **13** B_{1b}, B_{1a} 9.78, 10.94; 13β-propionate-7-OH **14** B_{1b}, B_{1a} 4.71, 4.8. ^{1}H NMR: δ 5.87 (dd, J = 14.8, 11.4, 1H), 5.68 (dt, J = 11.4, 2.1, 1H), 5.47 (d, J = 1.6, 1H), 5.45 (om, 1H), 5.35 (dd, J = 14.8, 10.0, 1H), 5.03 (d, J = 10.4, 1H), 4.79 (m, 1H), 4.67 (dd, J = 14.3 2.2, 1H), 4.58 (dd, J = 14.3, 2.0, 1H), 4.40 (m, 1H), 3.81 (d, J = 5.2, 1H), 3.63 (m, 1H), 3.23 (q, J = 2.2, 1H), 3.16 (d, J = 7.4, 1H), 2.59 (m, 1H), 2.42−2.21 (om, 5H), 1.79 (br s, 3H), 1.74 (om, 1H), 1.63−1.35 (om, 8H), 1.57 (s, 3H), 1.19−1.13 (om, 1H), 1.15 (t, J = 7.6, 3H), 1.04 (d, J = 6.6, 3H), 1.01−0.83 (om, 4H), 0.94 (s, 9H), 0.86 (d, J = 6.8, 3H), 0.80 (m, 3H), 0.14_4 (s, 3H), 0.14_0 (s, 3H), 0.13 (s, 9H). ^{13}C NMR: δ 173.7, 170.6, 141.2, 137.0, 135.7, 134.3, 126.2, 124.5, 120.8, 120.3, 97.5, 83.6, 83.4, 80.8, 77.1, 69.4, 69.1, 67.3, 67.1, 47.3, 41.9, 39.8, 36.4, 35.6_5, 35.5_7, 34.5, 31.3, 28.1, 27.9, 27.4, 25.9 (3C), 20.0, 19.0, 18.4, 17.5, 12.5, 11.7, 11.1, 9.2, 2.3 (3C), −4.5, −4.7. Anal. Calcd for $C_{46}H_{76}O_9Si_2$: C, 66.63; H, 9.24. Found: C, 66.64; H, 9.34.

13β-Hydroxy-5-*O*-TBDMS-7-*O*-TMS-22,23-dihydroavermectin B_1 Aglycon (15). A solution of propionate **13** (50 g, 0.06 mol) in *i*-PrOH (0.95 L) and titanium isopropoxide (56 mL, 0.188 mol) was heated at 80 °C for 12 h. The reaction mixture was cooled to 25 °C, diluted with ethyl acetate (2.5 L), and washed successively with 2% aqueous H_3PO_4 (2 × 2.5 L), 10% aqueous NaCl (1 L), 5% $NaHCO_3$ (2.5 L), and 10% aqueous NaCl (2.5 L). The organic layer was dried over magnesium sulfate (80 g), filtered, and concentrated *in vacuo* to give 45 g of crystalline 13-*epi*-OH-7-*O*-TMS-5-*O*-TBS-22,23-dihydroavermectin aglycon (**15**) in 95% yield (94.3 wt % assay, HPLC). HPLC: gradient elution, A:B, 90:10 to 100:0 in 30 min, t_R(min) 13β-propionate **13** B_{1b}, B_{1a} 10.05, 11.21; 13-*epi*-alcohol **15** B_{1b}, B_{1a} 4.87, 5.85.

Recrystallization. Alcohol **15** (40 g, 94.3 wt % assay), acetonitrile (795 mL), and water (34 mL) were heated to dissolve at 80 °C for 15 min. The mixture was cooled slowly to 70 °C, seeded with crystalline alcohol **15** (250 mg), further cooled to 0 °C over 2 h, and then aged at 0 °C for 24 h. Product was filtered, washed with cold CH_3CN:H_2O (400 mL, 60:40), and dried *in vacuo* (25 °C, 24 h), yielding alcohol **15** as a crystalline white solid (30.4 g, 80% yield) with a purity of 99.15 wt % (HPLC assay), mp 192−194 °C. A second crop was obtained by seeding the mother liquors and stirring for 24 h at 0 °C, yielding an additional 6.57 g for a combined recovery of 37.0 g (95% yield). ^{1}H NMR: δ 5.84 (dd, J = 14.9, 11.5, 1H), 5.65 (dt, J = 11.5, 2.4, 1H), 5.47 (q, J = 1.6, 1H), 5.33 (dd, J = 14.9, 9.9, 1H), 5.29 (om, 1H), 4.79 (m, 1H), 4.68 (dd, J = 14.3, 2.4, 1H), 4.57 (dd, J = 14.3, 2.4, 1H), 4.39 (m, 1H), 3.80 (d, J = 5.2, 1H), 3.77 (d, J = 9.9, 1H), 3.62 (m, 1H), 3.23 (q, J = 2.4, 1H), 3.17 (d, J = 7.5, 1H), 2.43−2.25 (om, 4H), 1.79 (s, 3H), 1.76 (om, 1H), 1.63−1.42 (om, 7H), 1.61 (s, 3H), 1.39 (m, 2H), 1.20−1.12 (om, 1H) 1.17 (d, J = 6.7, 3H), 0.94−0.84 (om, 4H), 0.94 (s, 9H), 0.86 (d, J = 6.7, 3H), 0.68 (m, 3H), 0.14_0 (s, 3H), 0.13_7 (s, 3H), 0.12 (s, 9H). ^{13}C NMR: δ 170.7, 140.7, 140.2, 138.2, 134.2, 123.8, 123.7, 121.0, 120.3, 97.5, 83.7, 83.4, 80.8, 77.1, 69.4, 69.1, 67.4, 67.3, 47.3, 41.9, 41.6, 36.3, 35.6_4, 35.5_9, 34.5, 31.2, 28.1, 27.4, 25.9 (3C), 20.0, 19.3, 18.4, 17.5, 12.5, 11.7, 10.6, 2.3 (3C), −4.5, −4.7. Anal. Calcd for $C_{43}H_{72}O_8Si_2$: C, 66.80; H, 9.39. Found: C, 66.69; H, 9.45.

13*β*-*O*-MOM-5-*O*-TBDMS-7-*O*-TMS-22,23-Dihydroavermectin B_1 Aglycon (16). A solution of chloromethylmethyl ether[15] (31.62 mL, 0.419 mol) and dichloromethane (116 mL) was cooled to −10 °C. DIPEA (75.3 mL, 0.433 mol) was added, and the solution was stirred at −10 °C for 45 min. The 13*β*-alcohol **15** (35.9, 0.046 mol) in dichloromethane (116 mL) was added at −10 °C, and the mixture was warmed to 25 °C and stirred for 23 h. The reaction mixture was cooled to −10 °C, 5% aqueous $NaHCO_3$ (0.5 L) was added, and the mixture was stirred for 30 min to destroy excess chloromethyl methyl ether. Ethyl acetate (2 L) was added, the phases were separated, and the aqueous layer was extracted with ethyl acetate (0.5 L). The combined organic layers were washed with 5% aqueous NaCl (0.5 L) and filtered through a silica gel pad (100 g, 230−400 mesh), and the eluent was concentrated *in vacuo* to afford 37.7 g of 13-*β*-MOM (**16**) in 98% yield with a purity of >99 area % by HPLC. HPLC: gradient elution, A:B, 90:10 to 100:0 in 30 min, t_R(min) alcohol **15** B_{1b}, B_{1a} 5.39, 6.37; 13*β*-*O*-MOM **16** B_{1b}, B_{1a} 11.42, 12.84. ^{1}H NMR: δ 5.83 (dd, J = 14.8, 1.4, 1H), 5.66 (dt, J = 11.4, 2.0, 1H), 5.46 (q, J = 1.6, 1H), 5.32 (om, 2H), 4.78 (m, 1H), 4.68 (dd, J = 14.3, 2.2, 1H), 4.63 (d, J = 6.7, 1H), 4.56 (dd, J = 14.3, 2.1, 1H), 4.45 (d, J = 6.7, 1H), 4.39 (m, 1H), 3.79 (d, J = 5.2, 1H), 3.68 (d, J = 10.0, 1H), 3.61 (m, 1H), 3.38 (s, 3H), 3.22 (q, J = 2.3, 1H), 3.15 (d, J = 7.4, 1H), 2.44 (om, 2H), 2.30 (m, 2H), 1.78 (om, 4H), 1.62 (dd, J = 9.8, 2.2, 1H), 1.56−1.44 (om, 5H), 1.51 (s, 3H), 1.37 (m, 2H), 1.17 (d, J = 6.5, 3H), 1.16 (om, 1H), 0.99−0.90 (om, 3H), 0.93 (s, 9H), 0.87 (om, 1H), 0.85 (d, J = 6.8, 3H), 0.78 (m, 3H), 0.14 (s, 3H), 0.13 (s, 3H), 0.12 (s, 9H). ^{13}C NMR: δ 170.7, 140.6, 138.2, 136.6, 134.2, 126.1, 123.8, 121.1, 120.3, 97.5, 92.8, 86.1, 83.4, 80.9, 77.0, 69.4, 69.1, 67.4, 67.2, 55.6, 47.3, 41.9, 40.4, 36.4, 35.6_3, 35.5_7, 34.5, 31.2, 28.1, 27.4, 25.9 (3C), 20.0, 19.5, 18.4, 17.5, 12.5, 11.7, 10.8, 2.3 (3C), −4.5, −4.7.

13-*β*-*O*-MOM-22,23-Dihydroavermectin B_1 Aglycon (2). A solution of 13*β*-*O*-MOM **16** (37.6 g, 0.046 mol) in MeOH (0.39 L), at 25 °C, was treated with 0.17 N methanolic HCl (13.4 mL) and stirred for 2.5 h at 25 °C. The reaction mixture was partitioned between 5% aqueous $NaHCO_3$ (0.5 L) and ethyl acetate (2.0 L), the phases were separated, and the aqueous layer was reextracted with ethyl acetate (0.5 L). The combined organic layers were washed with 5% aqueous NaCl (0.5 L) and concentrated *in vacuo* to afford 29.3 g of L-694,554, **2**, as an amorphous solid in 98% yield. HPLC: gradient elution, A:B, 60:40 to 80:20 in 18 min; 2.0 mL/min, t_R(min) L-694,554 (**2**) B_{1b}, B_{1a} 8.15, 9.91. ^{1}H NMR: δ 5.81−5.76 (om, 2H), 5.43 (br s, 1H), 5.40−5.21 (om, 3H), 4.70 (m, 2H), 4.66 (d, J = 6.7, 1H), 4.44 (d, J = 6.7, 1H), 4.30 (m, 1H), 3.97 (d, J = 6.2, 1H), 3.96 (s, 1H), 3.64 (d, J = 10.0, 1H), 3.61 (om, 1H), 3.38 (s, 3H), 3.28 (q, J = 2.2, 1H), 3.17 (d, J = 7.7, 1H), 2.44 (m, 1H), 2.36 (d, J = 8.1, 1H), 2.33 (m, 2H), 2.02 (m, 1H), 1.88 (s, 3H), 1.72−1.60 (om, 2H), 1.58-1.37 (om, 7H), 1.50 (s, 3H), 1.32 (t, J = 11.7, 1H), 1.15 (d, J = 6.5, 3H), 0.96 (t, J = 7.4, 3H), 0.90−0.84 (om, 1H), 0.86 (d, J = 6.8, 3H), 0.80 (m, 3H). ^{13}C NMR: δ 173.5, 140.3, 139.0, 137.9, 136.5, 125.8, 123.9, 120.4, 118.3, 97.5, 92.8, 85.8, 80.3, 79.4, 77.3, 68.7, 68.6, 67.7, 67.0, 55.7, 45.7, 41.4, 40.6, 36.7, 35.8, 35.5, 34.5, 31.3, 28.1, 27.5, 20.0, 19.1, 17.5, 12.6, 11.9, 10.7. HRMS: $[M + H]^+$ = 631.3839 (calculated = 630.3846).

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **1**, **2**, **6**, **7**, **8**, **9**, **13**, **15**, and **16** (18 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.

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