Syntheses and Biological Activities of 13-Substituted Avermectin Aglycons

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The reactions of sulfonate esters of the allylic/homoallylic 13-alcohol of 5-*O*-(*tert*-butyldimethylsilyl)-22,23-dihydroavermectin B_{1a} aglycon (**1a**) were investigated. Nucleophilic substitution gave 13β-chloro (**2**) and 13β-iodo derivatives (**4**), while solvolytic reaction conditions yielded 13α-methoxy (**9**), 13α-fluoro (**14**), and 13α-chloro products (**13**). A mixture of 13α- (**14**) and 13β-fluorides (**15**) was obtained upon reaction with DAST. The 13β-iodide (**4**) gave, upon elimination with lutidine, the 8(9),10(11),12(13),14(15)-tetraene (**6**). The 13β-alcohol (**7**) and the rearranged 15-ol 13(14)-ene (**7c**) and 15-amino 13(14)-ene derivatives (**5**) were obtained by substitution via the allylic carbonium ion. MEM ethers **11** and **12** of the two epimeric 13-ols were prepared by alkylation with MEM chloride. In contrast, methylation of **1a** with MeI and Ag_2O in CH_2Cl_2 occurred exclusively at the tertiary 7-hydroxy group and not at the secondary 13α-ol. Oxidation of the allylic alcohol **1a** proceeded under Swern conditions but not with MnO_2 to the 13-oxo aglycon (**16**), which was reduced by $NaBH_4$ exclusively to the natural 13α-ol (**1**), while reductive amination with $NaCNBH_3$–NH_4OAc gave the 13α-amine (**18**). The methoxime derivative (**17**) was obtained in the form of the two geometric isomers. Anthelmintic activities against the sheep nematode *Trichostrongylus colubriformis*, miticidal activities against the two-spotted spider mite (*Tetranychus urticae*), and insecticidal activities against the southern armyworm (*Spodoptera eridania*) as well as the binding constants to a free living nematode (*Caenorhabditis elegans*) derived receptor assay were obtained and compared to avermectin B_{1a}, 22,23-dihydroavermectin B_{1a} (**19b**, ivermectin), and the 13-deoxy-22,23-dihydroavermectin B_1 aglycon (**3b**) related to the milbemycins. None of the newly prepared derivatives exceeded the potency of the three reference compounds. Lipophilic 13-substituents such as halogen, alkoxy, and methoxime retained high biological activities in all assays, while the more polar substituents hydroxy and amino had weaker activities. Rearranged 15-substituted 13(14)-ene derivatives were completely inactive. The 13-oxo and the 12,13-dehydro analogues were only weakly active in vivo despite having good binding affinity to the receptor, possibly due to instability or poor absorption.

The avermectins and the milbemycins are 16-membered macrocylic lactones with closely related chemical structures and similar biological activities.[1a,b] 22,23-Dihydroavermectin B_1 (**19b**, ivermectin), a semisynthetic derivative of the avermectins, is widely used as a highly potent and broad-spectrum antiparasitic agent in veterinary practice (Chart I). Avermectin B_1 (abamectin) is under development as a pesticide for certain agricultural crops. The major structural difference between the avermectins and the milbemycins lies in the substituent attached to the 13-position of the macrocycle. The avermectins have an oleandrosyloleandrose substituent which appears to contribute to their high potency. Further substitution of the oleandrose disaccharide at the 4″-position is compatible with high biological activities.[2] The milbemycins on the other hand are unsubstituted at the 13-position. Sequential removal of the oleandrose substituents from the avermectins gave derivatives containing a single oleandrosyl or a hydroxy substituent at the 13-position.[3,4] The monosaccharides retained high anthelmintic activities, but the aglycons were much less active. It appears that a 13-hydroxy group is detrimental to the biological activities of avermectins and milbemycins, since the C13-unsubstituted 13-deoxyaglycons and milbemycins are potent anthelmintic agents. Therefore we were interested to study the effect of various 13-substituents on the anthelmintic and insecticidal activities of avermectin aglycons.

An interesting structural feature of the avermectin aglycons is the 13-hydroxy group, which is allylic with respect to the 14(15)-ene and homoallylic to the 10(11)-double bond of the 8(9),10(11)-diene. Furthermore, since this allylic–homoallylic alcohol is part of a 16-membered lactone ring, it is conformationally rigidly fixed. The X-ray structures of avermectin B_{1a} and of avermectin B_{2a} aglycon show O-13, C_{13}, C_{14}, C_{14a}, and C_{15} practically in one plane, which positions the π orbitals of the allylic double bond orthogonal to the σ bond of any 13α leaving group.[5] This precludes any contribution of the allylic double bond in a reaction of a 13-*O*-substituted avermectin aglycon. One could therefore expect reactions of 13α-substituted derivatives to proceed as at saturated carbon, possibly effected by neighboring-group participation of the 10(11)-ene. In contrast, a 13β-substituted derivative is conformationally correct for participation of the 14(15)-ene π electrons and should therefore react more like an allylic compound. An additional factor in the course of these reactions is the apparent steric hindrance observed during reactions of the aglycon containing the natural 13α-hydroxy group. For instance, aglycon **1b** forms readily only the 5-*O*-mono-TBDMS derivative **1a**, and it gives upon MnO_2 oxidation the 5-monooxo analogue exclusively. For these reasons we explored the chemical reactivity of this aglycon. Furthermore, intersting bioactivities could also be expected for the variously C_{13}-substituted avermectin aglycon derivatives. In order to simplify the chemistry of this multifunctional compound, we used the readily available protected 5-*O*-(*tert*-butyldimethylsilyl)-22,23-dihydroavermectin B_{1a} aglycon (**1a**) as starting material. The protecting group was removed from the final products, since a free 5-hydroxy group is required for high biological activities.

As described previously,[6] reaction of **1a** with 2-nitrobenzenesulfonyl chloride, 4-(dimethylamino)pyridine, and

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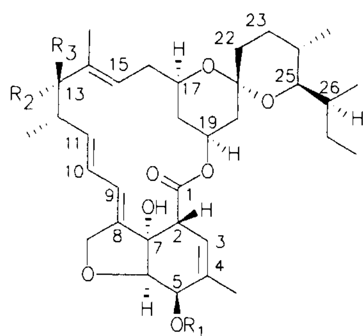
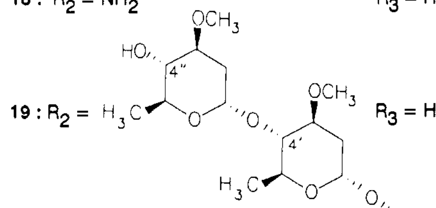
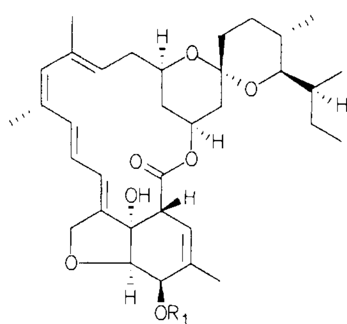
Chart I



a : $R_1 = Si(CH_3)_2C(CH_3)_3$
b : $R_1 = H$

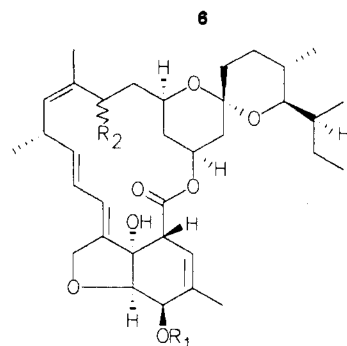
1 : $R_2 = OH$	$R_3 = H$	
2 : $R_2 = H$	$R_3 = Cl$	
3 : $R_2 = H$	$R_3 = H$	
4 : $R_2 = H$	$R_3 = I$	
7 : $R_2 = H$	$R_3 = OH$	
8 : $R_2 = OTS$	$R_3 = H$	
9 : $R_2 = OCH_3$	$R_3 = H$	
10 : $R_2 = OH$	$R_3 = H$	C_7OCH_3
11 : $R_2 = OCH_2OCH_2CH_2OCH_3$	$R_3 = H$	
12 : $R_2 = H$	$R_3 = OCH_2OCH_2CH_2OCH_3$	
13 : $R_2 = Cl$	$R_3 = H$	
14 : $R_2 = F$	$R_3 = H$	
15 : $R_2 = H$	$R_3 = F$	
16 : $R_2,R_3 = O$		
17 : $R_2,R_3 = NOCH_3$		
18 : $R_2 = NH_2$	$R_3 = H$	
19 : $R_2 =$ (structure below)	$R_3 = H$	





a : $R_1 = Si(CH_3)_2C(CH_3)_3$
b : $R_1 = H$

6



5 : $R_2 = N(CH_3)COCH_3$
7c : $R_2 = OH$ $R_1 = H$
9c : $R_2 = OCH_3$ $R_1 = H$

N,N-diisopropylethylamine in CH_2Cl_2 gave the 13β-chloride **2a**, presumably through an S_N2 reaction via the reactive 2-nitrobenzenesulfonate intermediate. The chloride **2a** was reduced with tributyltin hydride to give a 13-deoxy aglycon **3b**, whose structure and stereochemistry were related to the milbemycins.[6] Since the chloro group of **2** obviously is derived from the chloride ions present in the reaction mixture, addition of an excess of the more nucleophilic iodide (as tetrabutylammonium iodide) to the reaction mixture gave the 13-iodide **4a** in good yield as expected.

Iodide **4a** served as an intermediate for further modifications. Substitution with methylamine proceeded under allylic rearrangement to give, after acetylation, product **5**. The structure of **5** was confirmed by proton NMR spectra, which showed a new vinylic proton at 5.29 ppm as a doublet; this was identified as the C_{13}-H by irradiation of the C_{12}-H at 3.00 ppm, which caused the collapse of the doublets at 5.29 ppm (C_{13}-H) and at 1.07 ppm (C_{12}-CH_3). Upon heating with collidine to 100 °C, the iodide **4** underwent dehydrohalogenation to the 8(9),10(11),12(13),14(15)-tetraene **6** of undetermined stereochemistry at the new 12(13)-double bond. This showed a UV absorption at 231 and 295 nm, and the NMR spectrum had a new vinylic proton at 5.96 ppm, and a vinylic methyl at 1.84 ppm, in place of C_{13}-H and C_{12}-CH_3.[7] As a byproduct, a compound isomeric with aglycon **1** was obtained, which was identified by mass and NMR spectra as the 13-*epi*-aglycon **7**, showing a characteristic doublet at 3.72 ppm for the 13α-H. It appeared that in the presence of moisture the allylic cation generated from the iodide was trapped by water in preference to proton abstraction from C_{12}. Upon heating of iodide **4a** with aqueous collidine, the *epi*-aglycon **7** was obtained in good yield. Only 13β-alcohol accompanied by a very small amount of rearranged 13(14)-en-15-ol was obtained from the reaction mixture, but no 13α-hydroxy epimer was detected.[8] Reactions of 13β-iodide **4a** with the more nucleophilic amines occurred only under allylic rearrangment leading to 13(14)-ene 15-amino derivatives **5**, which were readily recognized by the shift of the now vinylic C_{13} proton doublet to 5.3 ppm.

While it was not possible to isolate the reactive 2-nitrobenzenesulfonate of **1a**, we did obtain the more stable tosylate **8a**. Attempted purification by silica gel column or thin-layer chromatography, however, resulted in solvolysis giving only starting material **1a**. Therefore crude **8a**, characterized by its NMR spectrum, was used for further reactions. Solvolysis in methanol containing $NaHCO_3$ gave the 13α-methoxy derivative **9a** almost exclusively, as shown by the ^1H NMR spectrum, with the characteristic broad singlet of the C_{13}-H at 3.4 ppm.[9,10] Retention of stereochemistry in this solvolysis is probably

(7) When a stronger base such as DBU was tried for this elimination, the 2,3-conjugated lactone analogue of **6** was obtained.
(8) Reaction of iodide **4a** with silver acetate in glacial AcOH, however, gives a mixture of 13- and 15-acetates.
(9) The shift of 3.43 ppm for **9b** appears high when compared to that for alcohol **1b** (4.00), 13-*O*-α-L-oleandrosyl-4′-*O*-α-L-oleandrosyl-**1b** (3.97), or 13-*O*-MEM ether **11a** (3.96). Comparison of ^1H and ^{13}C NMR spectra of **1b** and **9b** reveals a very close relationship; the only difference in the ^1H NMR spectrum of **9b** besides the 0.6 ppm upfield shift of C_{13}-H is a 0.1 ppm upfield shift of C_{15}-H, and the two ^{13}C NMR spectra are virtually identical (within 0.7 ppm) except for a shift of C_{13} (from 77.8 to 88.2 ppm, **1b** and **9b**, respectively) and the new CH_3O group at 58.2.
(10) During the PTLC purification of **9b**, a very small amount of the allylic rearrangment product **9c** was isolated: 400-MHz ^1H NMR ($CDCl_3$) δ 5.26 (1 H, dt, J = 9.0, 1.0, $C_{13}H$), 3.60 (1 H, br m, $C_{15}H$), 3.10 (1 H, m, $C_{12}H$).

due to the formation of a homoallylic cation intermediate. It is interesting to note that this 13-*O*-methyl derivative could not be obtained through methylation of **1a**, which gave under methyl iodide–silver oxide reaction conditions exclusively the 7-*O*-methyl isomer **10a**. The structure of **10a** was confirmed by the characteristic shift of the C_7 carbon in the ^{13}C NMR spectrum from 80.5 ppm of the alcohol to 86.1 ppm of the ether. In contrast, however, alkylation with 2-methoxyethoxymethyl chloride (MEM chloride) proceeded normally and gave the expected epimeric 13-*O* products **11a** and **12a** from **1a** and **7a**, respectively. Tosylate **8a** gave under solvolytic conditions in the presence of HCl the 13α-chloride **13a** epimeric with **2a**, while solvolysis in a HF–THF–pyridine mixture gave the 13α-fluoride **14b** as major and the 13β-fluoride **15b** as minor products. 13-Fluoro derivatives, however, were obtained more conveniently by the reaction of aglycon **1a** with (diethylamido)sulfur trifluoride (DAST) as a mixture of 13α- and 13β-fluorides **14a** and **15a**.

Oxidation of the allylic alcohol **1a** with MnO_2 was not successful, but Swern oxidation (oxalyl chloride–DMSO–Et_3N) gave ketone **16a** in good yield. Reduction of **16a** with $NaBH_4$ regenerated the 13α aglycon **1a** stereospecifically. Reductive amination of **16a** with $NaCNBH_3$–NH_4OAc gave principally the 13α-amino derivative **18a**, together with a small amount of the 13β-amino epimer. The methoxime **17a** was formed from the ketone as a mixture of its two geometrical isomers.

Biological Activities

The biological activities of the new aglycon derivatives were compared against those of avermectin B_1 or ivermectin in assays against the two-spotted spider mite *Tetranychus urticae* on bean plants,[11] against the sheep parasite *Trichostrongylus colubriformis* in a gerbil in vivo model,[12] and against neonate southern armyworm *Spodoptera eridania* larvae on bean leaves treated with the test compounds.[13] Comparative binding was measured by displacement of [22,23$^3H_2$]ivermectin to an avermectin receptor preparation derived from the free living nematode *Caenorhabditis elegans*[14] (Table I).

Structure–Activity Relationship

Avermectin B_1, ivermectin, and the 13-deoxy aglycon (milbemycin) structural types clearly have the most potent anthelmintic and miticidal activities (Table I). However, the relatively low potency of avermectin B_1 toward larvae of the lepidopteran southern armyworm is noteworthy. Potent antiparasitic and insecticidal activities were also shown by 13-halogen, by 13-*O*-MEM, which could be regarded as an oleandrose mimic, and by 13-methoxime derivatives. The 13-oxo analogue had only moderate anthelmintic activities despite very strong receptor binding. The 12,13-dehydro analogue, even more surprisingly, showed excellent receptor binding but no significant in vivo biological activity. This could be due to either chemical or metabolic instability. Substitution of the 13-position by the polar hydroxy and amino groups considerably reduces their bioactivities. Of the 13-epimeric aglycons, the β-substituted one appears to have a slight advantage over the natural α-epimer, and this trend is also shown by the more potent epimeric pair of 13-*O*-(methoxyethoxy)methyl derivatives. The simpler 13α-methoxy analogue was less potent than the larger ethers. Compounds that do not bind to the *C. elegans* receptor preparation, such as all the rearranged 13(14)-ene 15-substitution products, are without any biological activities. It is reasonable to suggest that, although receptor binding ranks intrinsic activity of these compounds, the system cannot predict fully in vivo activities due to variations in uptake and metabolism of the individual compounds.

Table I. Biological Activities of 13-Substituted 22,23-Dihydroavermectin B_{1a} Aglycons

C_{13}-substituent	*C. elegans* receptor K_i, nM	*T. colubriformis* ED_{90}, mg/kg	*T. urticae* EC_{90}, ppm	southern armyworm ED_{90}, ppm
avermectin B_1	0.1	0.03	0.05	8.0
19b: ivermectin	0.3	0.05	0.05	8.0
3b: H_2	0.9	0.06	0.05	0.5
6b: 12,13-didehydro	0.8	>2.5	>6.25	>1.0
1b: α-OH	6.4		0.5	>6.25
7b: β-OH	2.0	<0.5	0.05	>8.0
16b: =O	0.6	0.5	6.25	>0.5
11b: α-OCH_2O-$CH_2CH_2OCH_3$	2.7	>0.1	0.05	<1.0
12b: β-OCH_2O-$CH_2CH_2OCH_3$	2.9	<0.1	0.01	>0.25
9b: α-OMe	0.6	0.5	1.00	–
13b: α-Cl		<0.1	>0.1	<1.0
2b: β-Cl	1.0	0.1	0.25	0.5
14b: α-F	0.2	<0.1	0.05	>0.5
15b: β-F	0.3	<0.1	0.01	0.5
4b: β-I	2.4	0.5	1.25	–
18b: α-NH_2	>100	0.5	>0.1	>1.0
17b: =$NOCH_3$	0.3	<0.1	0.05	0.5
$\Delta^{13,14}$-15-morpholinyl	>100	>2.5	6.25	–
5b: $\Delta^{13,14}$-15-$N(CH_3)COCH_3$	>100	>2.5	>6.25	–
7c: $\Delta^{13,14}$-15-OH	>100	–	>6.25	–

Experimental Section

Progress of reactions and purity of products were determined by analytical TLC on silica gel plates, visualized by UV fluorescence and staining with phosphomolybdic acid, and by analytical HPLC on a Whatman Partisil 10 ODS-3 C_{18} reverse-phase column using UV absorption at 245 nm for detection. Products were purified by preparative thin-layer chromatography (PTLC) on 20 × 20 cm silica gel GF Uniplates (Analtech 0.25–1.0-mm thickness), by silica gel column (E. Merck 60, 70–230 mesh), and/or by reverse-phase high-performance liquid chromatography (HPLC) using a Whatman Partisil M20 10/50 ODS-3 column. Products were lyophilized from C_6H_6 and often retained C_6H_6 or H_2O as a partial solvate. ^1H and ^{13}C NMR spectra were recorded on Varian XL-200 and XL-400 instruments in $CDCl_3$ solution with Me_4Si as internal reference. Mass spectra were obtained on LKB Model 9000 or Varian MAT 212 mass spectrometers.

General Procedure A for Removal of the 5-*O*-*tert*-Butyldimethylsilyl Group. 13-Deoxy-22,23-dihydro-13β-chloroavermectin B_{1a} Aglycon (2b). A solution of **2a**[6] (130 mg) in MeOH (12 mL) containing 1.0% of *p*-toluenesulfonic acid monohydrate (120 mg) was left at 18 °C for 30–45 min, dilute aqueous $NaHCO_3$ then was added, and the product was extracted with EtOAc. The extract was washed with H_2O, dried, and concentrated in vacuo to a light glass. Purification by preparative TLC (1.5-mm thickness, 95:5 EtOAc–EtOH, three consecutive developments) gave 71 mg of **2b** as white foam: HPLC (85:15 MeOH–H_2O, 1.0 mL/min) t_R 17.6 min (94%); UV (MeOH) λ_{max} 243 nm (ϵ 28750); HRMS *m/e* (M^+) calcd for $C_{34}H_{49}O_7Cl$ 604.3167, found 604.3166; 200-MHz ^1H NMR ($CDCl_3$) δ 4.32 (1 H, t, J = 7.5 Hz, C_5H), 4.13 (1 H, d, J = 12 Hz, $C_{13}H$), 4.01 (1 H, s, C_7OH), 3.99 (1 H, d, J = 7.5 Hz, C_6H), 3.62 (1 H, m, $C_{17}H$), 3.30 (1 H, q, J = 2 Hz, C_2H), 3.20 (1 H, d, J = 9 Hz, $C_{25}H$), 2.59 (1 H, m, $C_{12}H$), 2.35 (1 H, d, J = 9 Hz, C_5OH).

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5-*O*-(*tert*-Butyldimethylsilyl)-13-deoxy-22,23-dihydro-13β-iodoavermectin B_{1a} Aglycon (4a). A solution of o-nitrobenzenesulfonyl chloride (5.2 g, 23.6 mmol) in CH_2Cl_2 (75 mL) was added dropwise during 40 min to a solution containing 1a (5.0 g, 7.14 mmol), *N,N*-diisopropylethylamine (4.41 g, 6.0 mL, 34.4 mmol), 4-(dimethylamino)pyridine (4.0 g, 32.7 mmol), and tetrabutylammonium iodide (10.0 g, 27 mmol) in CH_2Cl_2 (100 mL) stirred at 23 °C. After 3 h, the reaction mixture was poured into dilute aqueous NaH_2PO_4 and extracted with CH_2Cl_2. The extract was washed with dilute aqueous NaH_2PO_4 and aqueous NaCl, dried over $MgSO_4$, and evaporated in vacuo to 17 g of brown foam. Chromatography (350 g of silica gel, CH_2Cl_2) gave 2.4 g of a crude product containing 9% of **2a** and 86% of 4a (HPLC, 95:5 MeOH–H_2O, 1.5 mL/min, t_R 8.7, 10.0 min, 9%, 86%). Preparative HPLC afforded the analytical sample **4a**: HPLC t_R 10.0 min (100%); UV (MeOH) λ_{max} 244 nm (ϵ 27 860); HRMS *m/e* calcd for $C_{40}H_{63}O_7ISi$ (M^+) 810.3386, found 810.3372; MS, *m/e* 810 (M^+), 753, 735, 682, 664, 643, 625, 568, 440; 200-MHz ^1H NMR ($CDCl_3$) δ 4.62 (1 H, d, J = 11.0 Hz, $C_{13}H$), 4.45 (1 H, m, C_5H), 4.03 (1 H, s, C_7OH), 3.83 (1 H, d, J = 6.0 Hz, C_6H), 3.38 (1 H, m, C_2H), 2.66 (1 H, m, $C_{12}H$), 1.52 (3 H, s, $C_{14}CH_3$), 1.23 (3 H, d, J = 7.0 Hz, $C_{12}CH_3$).

13-Deoxy-22,23-dihydro-13β-iodoavermectin B_{1a} Aglycon (4b). Reaction of 4a (150 mg) according to general procedure A and purification by preparative HPLC (9:1 MeOH–H_2O, 8 mL/min) gave 80 mg of 4a: HPLC (9:1 MeOH–H_2O, 1.0 mL/min) t_R 11.0 min (100%); UV (MeOH) λ_{max} 243 nm (ϵ 27 700); HRMS *m/e* calcd for $C_{34}H_{49}IO_7$ (M^+) 696.2523, found 696.2524; 200-MHz ^1H NMR ($CDCl_3$) δ 4.63 (1 H, d, J = 12 Hz, $C_{13}H$), 4.34 (1 H, t, J = 7.5 Hz, C_5H), 4.03 (1 H, s, C_7OH), 3.99 (1 H, d, J = 7.5 Hz, C_6H), 3.60 (1 H, m, $C_{17}H$), 3.30 (1 H, q, J = 2 Hz, C_2H), 3.20 (1 H, d, J = 9 Hz, $C_{25}H$), 2.67 (1 H, m, $C_{12}H$), 2.35 (1 H, d, J = 9 Hz, C_5OH).

5-*O*-(*tert*-Butyldimethylsilyl)-13-dehydro-13-deoxy-15,22,23-trihydro-15-(*N*-acetyl-*N*-methylamino)avermectin B_{1a} Aglycon (5a). A slow stream of methylamine was bubbled into a solution of **4a** (100 mg, 0.123 mmol) in 10 mL of CH_2Cl_2 for 15 min at room temperature, and the solution was left for 18 h in a stoppered flask. Then the reaction mixture was concentrated in vacuo to dryness; the residue was dissolved in CH_2Cl_2 and purified by preparative TLC (1.0-mm SiO_2 layer, 95:5 CH_2Cl_2–MeOH) to give 58 mg of 5-*O*-(*tert*-butyldimethylsilyl)-13-dehydro-13-deoxy-15,22,23-trihydro-15-(*N*-methylamino)avermectin B_{1a} aglycon as a white foam: TLC (95:5 CH_2Cl_2–MeOH) R_f 0.30; MS, *m/e* 713 (M^+), 471 (retro Diels–alder product); 300-MHz ^1H NMR ($CDCl_3$) (shows impurities) δ 2.29 (3 H, s, NCH_3). To facilitate further purification and characterization, we acetylated 25 mg of the product (0.5 mL of CH_2Cl_2, 6 drops of pyridine, 3 drops of Ac_2O, 0 °C, 30 min). Addition of EtOAc, washing with water, drying, and concentration in vacuo gave 30 mg of crude **5a**. Purification by preparative TLC (1.0-mm SiO_2 layer, 1:1 CH_2Cl_2–EtOAc) gave 20 mg of still impure **5a** as a white glass: HPLC (54:36:10 CH_3CN–MeOH–H_2O, 1.5 mL/min) t_R 11.0, 12.3 min (25, 75%). Final purification by preparative HPLC (92:8 MeOH-H_2O) gave 11 mg of **5a**: HPLC (54:36:10 CH_3CN–MeOH–H_2O, 1.5 mL/min) t_R 13.3 min (95%); UV (MeOH) λ_{max} 251 nm (ϵ 26 120); HRMS *m/e* found 755.4791 (M^+), calcd for $C_{43}H_{69}NO_8Si$ 755.4788; 400-MHz ^1H NMR ($CDCl_3$, 26 °C) δ 5.80 (1 H, br m, $C_{10}H$), 5.68 (1 H, dt, J = 12, 2.2 Hz, C_9H), 5.34 (1 H, m, C_3H), 5.31 (1 H, br m, $C_{13}H$), 5.24 (1 H, dd, J = 14, 9 Hz, $C_{11}H$), 5.00 (1 H, br m, $C_{15}H$), 4.84 (1 H, br m, $C_{19}H$), 4.68 (1 H, dd, J = 14.5, 2.2 Hz, $C_{8a}H$), 4.56 (1 H, dd, J = 14.5, 2.2 Hz, $C_{8a}H$), 4.44 (1 H, d, J = 5.5 Hz, C_5H), 3.94 (1 H, s, C_7OH), 3.89 (1 H, d, J = 5.5 Hz, C_6H), 3.52 (1 H, br m, $C_{17}H$), 3.37 (1 H, q, J = 2 Hz, C_2H), 2.95 (3 H, s, NCH_3), 2.09 (3 H, s, $COCH_3$), 1.79 (3 H, s, C_4CH_3), 1.59 (3 H, s, $C_{14}CH_3$), 1.09 (3 H, d, J = 6.5 Hz, $C_{12}CH_3$); 400-MHz ^1H NMR ($CDCl_3$, -5 °C) δ 5.29 (1 H, d, J = 14 Hz, $C_{13}H$), 4.97 (1 H, d, J = 10 Hz, $C_{15}H$), 3.00 (1 H, m, $C_{12}H$), 2.94 and 2.91 (3 H, 2 s, NCH_3), 2.10 and 2.08 (3 H, 2 s, $COCH_3$), 1.56 and 1.55 (3 H, 2 s, $C_{14}CH_3$), 1.07 (3 H, m, $C_{12}CH_3$); irradiation at -5 °C of $C_{12}H$ causes changes of $C_{13}H$, $C_{11}H$, and $C_{12}CH_3$, but not $C_{15}H$.

13-Dehydro-13-deoxy-15,22,23-trihydro-15-(*N*-acetyl-*N*-methylamino)avermectin B_{1a} Aglycon (5b). Compound **5a** (25 mg) was deprotected according to general procedure A and purified by preparative TLC (CH_2Cl_2–MeOH, 95:5) to give 10 mg of white foam: UV (MeOH) λ_{max} 251 nm (ϵ 26 220); HRMS *m/e* found 641.3905 (M^+); calcd for $C_{37}H_{54}NO_8$ 641.3924; 300-MHz ^1H NMR ($CDCl_3$, 25 °C) in close agreement with **5a** except for the absence of *tert*-butyldimethylsilyl peaks and the minor expected shifts for C_3H, C_5H, C_6H, $C_{8a}CH_2$ peaks (δ 5.45, 4.30, 4.05, 4.70, respectively).

5-*O*-(*tert*-Butyldimethylsilyl)-12,13-didehydro-13-deoxy-22,23-dihydroavermectin B_{1a} Aglycon (6a). A solution of a mixture (902 mg) containing 70% of 13β-iodo **4a** and 15% of 13β-chloro **2a** in 5.3 mL of 2,6-lutidine was heated under N_2 at 100 °C for 14.5 h, when TLC (20:80 Et_2O–petroleum ether) indicated completion. The solution was evaporated to dryness in vacuo. The solid residue was extracted with Et_2O. Insolubles were removed by filtration, and the ether solution was evaporated in vacuo, furnishing 1.1 g of solids containing 33% of 12(13)-ene **6a**, 46% of 13β-ol **7a**, and 11% of 13β-chloride **2a** (HPLC, 95:5 MeOH–H_2O, 1.5 mL/min, t_R 10.7, 4.7, and 8.4 min, respectively). This mixture was chromatographed on a column of silica gel (99:1 CH_2Cl_2–MeOH) and separated into two major bands. The faster band (350 mg) contained 66% of **6a** and 29% of **2a** (HPLC t_R 10.7, 8.4 min), and the slower band (370 mg) contained mainly **7a** (see below). An aliquot of 97 mg of the faster band (350 mg) containing **6a** and **2a** was purified by preparative HPLC (95:5 MeOH–H_2O, 5.0 mL/min), furnishing 57 mg of **6a**: HPLC (95:5 MeOH–H_2O, 1.5 mL/min) t_R 6.52 min (100%); MS, *m/e* 682 (M^+), 664, 625, 607, 440, 223, 195, 171; 200-MHz ^1H NMR ($CDCl_3$) δ 6.56 (1 H, d, J = 14.0 Hz, $C_{11}H$), 5.99 (1 H, dd, J = 14.0, 11.0, $C_{10}H$), 5.96 (1 H, br s, $C_{13}H$), 5.87 (1 H, dt, J = 11.0, 2.0 Hz, C_9H), 4.61 (2 H, m, $C_{8a}CH_2$), 4.48 (1 H, m, C_5H), 4.38 (1 H, s, C_7OH), 3.84 (1 H, d, J = 5.4 Hz, C_6H), 3.38 (1 H, q, J = 2.2 Hz, C_2H), 1.84 (3 H, s, $C_{12}CH_3$), 1.80 (3 H, s, C_4CH_3), 1.63 (3 H, s, $C_{14}CH_3$).

12,13-Didehydro-13-deoxy-22,23-dihydroavermectin B_{1a} Aglycon (6b). Compound **6a** (52.5 mg) was deblocked according to general procedure A and purified by preparative TLC on silica gel (Et_2O–petroleum ether, 30:70), furnishing 38.5 mg of **6b**: HPLC (85:15 MeOH–H_2O, 1.5 mL/min) t_R 11.6 min (100%); UV (MeOH) λ_{max} 231, 295 nm (ϵ 13 200, 20 700); HRMS *m/e* found 568.3406, calcd for $C_{34}H_{48}O_7$ 568.3400; MS, *m/e* 568 (M^+), 550, 511, 440, 223, 195, 111; 200-MHz ^1H NMR ($CDCl_3$) δ 6.44–6.65 (1 H, m, $C_{11}H$), 5.85–6.03 (3 H, m, C_9H, $C_{10}H$, $C_{13}H$), 5.47 (1 H, br s, C_3H), 4.37 (1 H, s, C_7OH), 4.35 (1 H, br t, J = 6.0 Hz, C_5H), 4.02 (1 H, d, J = 6.0 Hz, C_6H), 3.34 (1 H, q, J = 2.2 Hz, C_2H), 1.86 (6 H, br s, C_4H_3 + $C_{12}CH_3$), 1.62 (3 H, s, $C_{14}CH_3$).

5-*O*-(*tert*-Butyldimethylsilyl)-22,23-dihydro-13-*epi*-avermectin B_{1a} Aglycon (7a). A solution of 4a (1.0 g, 1.2 mmol) in 2,6-lutidine (6.0 mL) and water (0.3 mL) was stirred at 100 °C for 18 h under N_2. The reaction mixture was concentrated under high vacuum, dissolved in ether, washed with dilute aqueous HCl, water, and aqueous NaCl, dried, and concentrated in vacuo to a dark oil (1.1 g). Column chromatography (SiO_2, 50 g, CH_2Cl_2–Et_2O, 97:3) gave 350 mg of **7a**: HPLC (95:5 MeOH–H_2O, 1.0 mL/min) t_R 6.6 min (98%); UV (MeOH) λ_{max} 245 nm (ϵ 25 200); HRMS *m/e* found 700.4373 (M^+), calcd for $C_{40}H_{64}O_8Si$ 700.4370; MS, *m/e* 700 (M^+), 6.82, 643, 625, 458, 440, 375, 307, 223, 195, 179, 151; 200-MHz ^1H NMR ($CDCl_3$) δ 4.44 (1 H, br s, C_5H), 3.83 (1 H, d, J = 5.5 Hz, C_6H), 3.72 (1 H, d, J = 10.0 Hz, $C_{13}H$), 3.37 (1 H, q, J = 2.2 Hz, C_2H), 2.36 (1 H, m, $C_{12}H$), 1.81 (3 H, s, C_4CH_3), 1.14 (3 H, d, J = 6.5 Hz, $C_{12}CH_3$).

22,23-Dihydro-13-*epi*-avermectin B_{1a} Aglycon (7b). Compound **7a** (710 mg) was deprotected according to general procedure A, giving 600 mg of crude **7b**, HPLC (45:30:25 CH_3CN–MeOH–H_2O, 1.5 mL/min) t_R 6.8, 7.8 min (19%, 81%). Preparative HPLC (80:20 MeOH–H_2O) gave 353 mg of **7b** (amorphous lyophilizate from benzene): HPLC t_R 7.8 min (100%), UV (MeOH) λ_{max} 245 nm (ϵ 30 120); HRMS *m/e* found 586.3513 (M^+), calcd for $C_{34}H_{50}O_8$ 586.3506; MS, *m/e* 586 (M^+), 568, 550, 529, 458, 440, 307, 261, 221; 300-MHz ^1H NMR ($CDCl_3$) δ 4.29 (1 H, t, J = 6.8 Hz, C_5H), 3.99 (1 H, s, C_7OH), 3.97 (1 H, d, J = 6.9 Hz, C_6H), 3.72 (1 H, dd, J = 10.4, 2 Hz, $C_{13}H$), 3.26 (1 H, q, J = 2 Hz, C_2H), 3.18 (1 H, d, J = 6.8 Hz, $C_{25}H$), 2.34 (1 H, d, J = 8.4, C_5OH).

13-Dehydro-13-deoxy-15-hydroxy-15,22,23-trihydroavermectin B_{1a} Aglycon (7c). The allylic rearrangement product of **7b** was isolated during its HPLC purification as a minor byproduct. Compound **7c**: HPLC t_R 6.8 min (100%); UV (MeOH) λ_{max} 251 nm (ϵ 26 490); HRMS *m/e* found 586.3513 (M^+), calcd for $C_{34}H_{50}O_8$ 586.3506; 300-MHz ^1H NMR ($CDCl_3$) δ 5.14 (1 H, d, J = 9.0 Hz, $C_{13}H$), 4.09 (1 H, dd, J = 11.2, 4.5, $C_{15}H$), remainder

of spectrum closely resembling **7b**.

5-*O*-(*tert*-Butyldimethylsilyl)-22,23-dihydro-13-*O*-(*p*-tolylsulfonyl)avermectin B_{1a} Aglycon (8a). A solution of **1a** (500 mg, 0.71 mmol), *N*,*N*-diisopropylethylamine (0.75 mL, 557 mg, 4.3 mmol), 4-(dimethylamino)pyridine (500 mg, 4.1 mmol), and *p*-toluenesulfonyl chloride (500 mg, 2.6 mmol) in 25 mL of CH_2Cl_2 was stirred at 18 °C under N_2 for 24 h. Then it was poured into ice-water and extracted with ether. This was washed repeatedly with aqueous, cold KH_2PO_4, $NaHCO_3$, and H_2O, dried, and concentrated in vacuo to 580 mg of crude **8a** as orange glass: HPLC (9:1 MeOH-H_2O, 1.0 mL/min) t_R 7.6, 8.9 min (13%, 74%); 200-MHz ^1H NMR ($CDCl_3$) δ 7.81 (2 H, d, J = 9 Hz, aromatic H), 7.34 (2 H, d, J = 9 Hz, aromatic H), 4.88 (1 H, br s, $C_{13}H$), 3.81 (1 H, d, J = 6 Hz, C_6H), 3.33 (1 H, m, C_2H), 2.45 (3 H, s, CH_3 of tosyl).

5-*O*-(*tert*-Butyldimethylsilyl)-22,23-dihydro-13-*O*-methylavermectin B_{1a} Aglycon (9a). A solution of crude **8a** (160 mg) and KOAc (450 mg) in 20 mL of MeOH was stirred at 18 °C for 2.5 h. The reaction mixture was poured into cold, dilute aqueous $NaHCO_3$ and extracted with ether. The extract was washed with water, dried, and concentrated in vacuo to 290 mg of orange oil. This was purified by preparative TLC (two 1.5-mm SiO_2 plates, CH_2Cl_2-Et_2O, 97:3) to give 70 mg of **9a** as light foam: HPLC (9:1 MeOH-H_2O, 1.0 mL/min) t_R 14.1 min (95%); UV (MeOH) λ_{max} 243 nm (ϵ 23600); HRMS m/e found 714.4533 (M^+), calcd for $C_{41}H_{66}O_8Si$ 714.4527; 200-MHz ^1H NMR ($CDCl_3$) δ 4.47 (1 H, m, C_5H), 4.13 (1 H, s, C_7OH), 3.84 (1 H, d, J = 6.0, C_6H), 3.39 (1 H, br s, $C_{13}H$), 3.36 (3 H, s, $C_{13}OCH_3$), 1.52 (3 H, s, $C_{14}CH_3$), 1.14 (3 H, d, J = 6.0, $C_{12}CH_3$).

22,23-Dihydro-13-*O*-methylavermectin B_{1a} Aglycon (9b). Compound **9a** (65 mg) was deprotected according to general procedure A and purified by repeated PTLC (CH_2Cl_2-EtOAc, 90:10, then CH_2Cl_2-MeOH, 98:2) to give 24 mg of white foam: HPLC (85:15 MeOH-H_2O, 1.0 mL/min) t_R 8.0, 9.4 min (10%, 82%); UV (MeOH) λ_{max} 243 nm (ϵ 26600); HRMS m/e found 600.3662 (M^+), calcd for $C_{35}H_{52}O_8$ 600.3662; 200-MHz ^1H NMR ($CDCl_3$) δ 5.19 (1 H, br d, J = 9 Hz, $C_{15}H$), 4.35 (1 H, br t, J = 6.0, C_5H), 4.13 (1 H, s, C_7OH), 4.01 (1 H, d, J = 6.0, C_6H), 3.32 (1 H, br m, $C_{17}H$), 3.43 (1 H, br s, $C_{13}H$), 3.39 (3 H, s, $C_{13}OCH_3$), 3.29, (1 H, br s, C_2H), 3.23 (1 H, d, J = 8.5, $C_{25}H$).

5-*O*-(*tert*-Butyldimethylsilyl)-22,23-dihydro-7-*O*-methylavermectin B_{1a} Aglycon (10a). Compound **1a** (200 mg, 0.285 mmol), CH_3I (1.0 mL), and freshly prepared Ag_2O (1.0 g) in 15 mL of dry Et_2O were stirred at 23 °C. After 5 days, additional amounts of CH_3I (0.5 mL) and Ag_2O (0.5 g) were added. After a total reaction time of 8 days, the mixture was filtered and the filtrate evaporated in vacuo. The residue was chromatographed on a column of silica gel (99.5:0.5 and 99:1.0 CH_2Cl_2-MeOH), furnishing 170 mg of **10a**: HPLC (95:5 MeOH-H_2O, 1.5 mL/min) t_R 6.22 min (65%). A portion (7.5 mg) was further purified by PTLC on silica gel (99.5:0.5 CH_2Cl_2-MeOH) by using multiple development, furnishing 3.8 mg of **10a**: HPLC purity >90%; MS, m/e 714 (M^+), 682, (M^+ - MeOH), 625 (M^+ - MeOH - C_4H_9), 472 (retro-Diels-Alder product), 454 (472 - H_2O); 200-MHz ^1H NMR ($CDCl_3$) δ 4.44 (1 H, m, C_5H), 4.10 (1 H, d, J = 6 Hz, C_6H), 4.07 (1 H, br s, $C_{13}H$), 3.32 (3 H, s, C_7OCH_3), 1.84 (3 H, s, C_4CH_3), 1.52 (3 H, s, $C_{14}CH_3$), 1.21 (3 H, d, J = 7.0 Hz, $C_{12}CH_3$). Anal. ($C_{41}H_{66}O_8Si$) C, H.

22,23-Dihydro-7-*O*-methylavermectin B_{1a} Aglycon (10b). Crude (60%) **10a** (55 mg) was deblocked according to general procedure A and purified by PTLC on silica gel (98.5:1.5 CH_2Cl_2-MeOH) by using multiple developments, furnishing 10.5 mg of **10b**: HPLC (90:10 MeOH-H_2O, 1.5 mL/min) t_R 4.0 min (90%); UV (MeOH) λ_{max} 244 nm (ϵ 27300); HRMS calcd for $C_{35}H_{52}O_8$ m/e 600.3662 (M^+), found 600.3656; 200-MHz ^1H NMR ($CDCl_3$) δ 4.25 (1 H, m, C_5H), 4.26 (1 H, m, C_6H), 4.03 (1 H, br s, $C_{13}H$), 3.32 (3 H, s, C_7OCH_3), 1.87 (3 H, s, C_4CH_3), 1.22 (3 H, d, J = 7.0 Hz, $C_{12}CH_3$).

5-*O*-(*tert*-Butyldimethylsilyl)-22,23-dihydro-13-*O*-[(2-methoxyethoxy)methyl]avermectin B_{1a} Aglycon (11a). (2-Methoxyethoxy)methyl chloride (400 μL, 3.5 mmol) was added to a solution of **1a** (250 mg, 0.35 mmol) and *N*,*N*-diisopropylethylamine (700 μL, 4.0 mmol) in dry CH_2Cl_2 (1.0 mL). The solution was stirred at 22 °C for 3 days, poured into aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by PTLC on silica gel (CH_2Cl_2-MeOH, 99:1, two elutions), furnishing 132 mg of **11a**: HPLC (95:5 MeOH-H_2O, 1.5 mL/min) t_R 8.16 min (97%); MS, m/e 788 (M^+), 770, 713, 682, 625; 200-MHz ^1H NMR ($CDCl_3$) δ 4.70 (4 H, m, $C_{8a}CH_2$ + $C_{13}OCH_2O$), 4.14 (1 H, s, C_7OH), 3.96 (1 H, br s, $C_{13}H$), 3.83 (1 H, d, J = 6.0 Hz, C_6H), 3.59 (4 H, m, OCH_2CH_2O), 3.41 (3 H, s, OCH_3), 3.37 (1 H, q, J = 2 Hz, C_2H), 2.54 (1 H, m, $C_{12}H$), 1.14 (3 H, d, J = 7 Hz, $C_{12}CH_3$). Anal. ($C_{44}H_{72}O_{10}Si$) C, H.

22,23-Dihydro-13-*O*-[(2-methoxyethoxy)methyl]avermectin B_{1a} Aglycon (11b). Compound **11a** (31 mg) was deblocked according to general procedure A and purified by PTLC on silica gel (CH_2Cl_2-MeOH, 98.5:1.5), furnishing 26 mg of **11b**: HPLC (90:10 MeOH-H_2O, 1.5 mL/min) t_R 5.28 min (100%); UV (MeOH) λ_{max} 246 nm (ϵ 30400); MS, m/e 656 (M^+ - H_2O) 568, 550; 200-MHz ^1H NMR ($CDCl_3$) δ 4.70 (4 H, m, $C_{8a}CH_2$ + $C_{13}OCH_2O$), 4.31 (1 H, br t, J = 6 Hz, C_5H), 4.10 (1 H, s, C_7OH), 3.98 (1 H, d, J = 6 Hz, C_6H), 3.96 (1 H, br s, $C_{13}H$), 3.71-3.55 (5 H, m, $C_{17}H$ + OCH_2CH_2O), 3.41 (3 H, s, OCH_3), 3.28 (1 H, q, J = 2.2 Hz, C_2H), 2.55 (1 H, m, $C_{12}H$), 1.16 (3 H, d, J = 7.0 Hz, $C_{12}CH_3$). Anal. ($C_{38}H_{58}O_{10}$) C, H.

5-*O*-(*tert*-Butyldimethylsilyl)-22,23-dihydro-13β-*O*-[(2-methoxyethoxy)methyl]avermectin B_{1a} Aglycon (12a). (2-Methoxyethoxy)methyl chloride (117 μL, 0.946 mmol) was added to **7a** (60 mg, 0.086 mmol) and *N*,*N*-diisopropylethylamine (195 μL, 1.12 mmol) in 0.24 mL of dry CH_2Cl_2. The solution was stirred at 40 °C for 16 h, poured into aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by two consecutive PTLC (CH_2Cl_2-MeOH, 98.5:1.5, and Et_2O-petroleum ether, 80:20), furnishing 30.5 mg of **12a**, which was lyophilized from benzene: HPLC (95:5 MeOH-H_2O, 1.5 mL/min) t_R 7.27 (98%); MS, m/e 788 (M^+), 770, 713, 682, 625; 200-MHz ^1H NMR ($CDCl_3$) δ 4.64 (4 H, m, $C_{8a}CH_2$ + $C_{13}OCH_2O$), 3.99 (1 H, s, C_7OH), 3.84 (1 H, d, J = 6.0 Hz, C_6H) 3.68 (1 H, d, J = 9.5 Hz, $C_{13}H$), 3.58 (4 H, m, OCH_2CH_2O), 3.42 (3 H, s, OCH_3), 2.43 (1 H, m, $C_{12}H$), 1.80 (3 H, s, C_4CH_3), 1.51 (3 H, s, $C_{14}CH_3$), 1.13 (3 H, d, J = 7.0 Hz, $C_{12}CH_3$). Anal. ($C_{44}H_{72}O_{10}Si \cdot 0.5C_6H_6$) C, H.

22,23-Dihydro-13β-*O*-[(2-methoxyethoxy)methyl]avermectin B_{1a} Aglycon (12b). Compound **12a** (26 mg) was deblocked according to general procedure A and purified by PTLC using multiple development (CH_2Cl_2-MeOH, 97.5:2.5), furnishing 24 mg of **12b**: HPLC (90:10 MeOH-H_2O) 1.5 mL/min) t_R 5.26 (93%); UV (MeOH) λ_{max} 243 nm (ϵ 31500); MS, m/e 674 (M^+), 568, 550; 200-MHz ^1H NMR ($CDCl_3$ + CD_3OD spike) δ 4.72 (2 H, br s, $C_{13}OCH_2O$), 4.31 (1 H, br d, J = 6 Hz C_5H), 3.77 (1 H, d, J = 6 Hz, C_6H), 3.70 (1 H, d, J = 10.0 Hz, $C_{13}H$), 3.58 (4 H, br s, OCH_2CH_2O), 3.42 (3 H, s, OCH_3), 3.28 (1 H, q, J = 2 Hz, C_2H), 2.43 (1 H, m, $C_{12}H$), 1.13 (3 H, d, J = 7.0 Hz, $C_{12}CH_3$). Anal. ($C_{38}H_{58}O_{10}$) C, H.

5-*O*-(*tert*-Butyldimethylsilyl)-13-deoxy-22,23-dihydro-13α-chloroavermectin B_{1a} Aglycon (13a). A solution of **1a** (100 mg, 0.143 mmol) and NEt_3 (72 mg, 0.1 mL, 0.71 mmol) in CH_2Cl_2 (2.0 mL) was stirred in an ice bath, while a solution of methanesulfonyl chloride (55 mg, 37 μL, 0.48 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise. After 4 h, the reaction mixture was added to a pH 7.0 aqueous phosphate buffer solution, which was extracted with ether. The ether extract was washed with water, dried, and concentrated in vacuo to 100 mg of a light foam: TLC (95:5 CH_2Cl_2-EtOAc) 2 major spots, R_f 0.1 and 0.35. Isolation of the faster band by preparative TLC (SiO_2, 1.5 mm thick, CH_2Cl_2, two consecutive developments) yielded 22 mg of **13a** as white amorphous powder: HPLC (9:1 MeOH-H_2O, 1.5 mL/min) t_R 22.3 min (single peak); MS, m/e 718/720 (M^+, Cl_1), 643/645 (M^+ - C_4H_9, -H_2O, Cl_1), 476/478 (retro-Diels-Alder product, Cl_1); 200-MHz ^1H NMR ($CDCl_3$) δ 4.46 (2 H, m, C_5H, $C_{13}H$), 3.44 (1 H, s, C_7OH), 3.11 (1 H, d, J = 6.0 Hz, C_6H), 3.71 (1 H, m, $C_{17}H$), 3.38 (1 H, q, J = 2 Hz, C_2H), 3.21 (1 H, d, J = 9 Hz, $C_{25}H$), 2.96 (1 H, m, $C_{12}H$).

13-Deoxy-22,23-dihydro-13α-chloroavermectin B_{1a} Aglycon (13b). Compound **13a** (20 mg) was deprotected according to general procedure A and purified by preparative TLC (CH_2Cl_2-EtOAc, 94:6) to give 15 mg of white foam: UV (MeOH) λ_{max} 244 nm (ϵ 30500); HRMS m/e found 604.3118 (M^+), calcd for $C_{34}H_{49}O_7Cl$ 604.3163; 200-MHz ^1H NMR ($CDCl_3$) δ 4.41 (1 H,

br s, $C_{13}H$), 4.31 (1 H, t, J = 7.5 Hz, C_5H), 4.11 (1 H, s, C_7OH), 3.98 (1 H, d, J = 7.5 Hz, C_6H), 3.71 (1 H, br m, $C_{17}H$), 3.27 (1 H, q, J = 2.0, C_2H), 3.20 (1 H, d, J = 11.0, $C_{25}H$), 2.80 (1 H, m, $C_{12}H$).

5-*O*-(*tert*-Butyldimethylsilyl)-13-deoxy-22,23-dihydro-13α- and -13β-fluoroavermectin B_{1a} Aglycons (14a and 15a). A solution of Et_2NSF_3 (2.0 mL, 2.44 g, 0.015 mol) in 80 mL of CH_2Cl_2 was stirred at −65 °C under N_2. To this was added dropwise a solution of 1a (10.0 g, 0.014 mol) in 80 mL of CH_2Cl_2 during 15 min. The course of the reaction was followed by TLC [SiO_2, hexane–EtOAc, 85:15, R_f(1a, 14a, 15a) 0.35, 0.59, 0.65]; the reaction mixture was stirred for 30 min at −65 °C and for 1 h at −20 °C and then allowed to come to 18 °C during 1.5 h. Then it was poured into dilute aqueous $NaHCO_3$, extracted with CH_2Cl_2, washed with H_2O, dried, and concentrated in vacuo to 9.2 g of light glass. Repeated column chromatographies on SiO_2 with hexane–EtOAc, 85:15, solvent gave 2.5 g of a mixture of 14a and 15a. This was separated by several passes through two cartridges of SiO_2 on a Waters PREP 500 apparatus into 1.22 g of 14a and 0.5 g of 15a. Compound 14a: light foam; HPLC (54:36:10 CH_3CN–MeOH–H_2O, 1.5 mL/min) t_R 14.0 min (99%); UV (MeOH) λ_{max} 243 nm (ε 28600); HRMS m/e found 702.4330 (M^+), calcd for $C_{40}H_{63}FO_7Si$ 702.4326; MS, m/e 702 (M^+), 460 (retro-Diels–Alder product); 200-MHz ^1H NMR ($CDCl_3$) δ 4.73 (1 H, br d, J = 48 Hz, $C_{13\beta}H$), 4.46 (1 H, br m, C_5H), 4.10 (1 H, s, C_7OH), 3.82 (1 H, d, J = 6.0 Hz, C_6H), 3.36 (1 H, q, J = 2.2 Hz, C_2H), 2.62 (1 H, br m, $C_{12}H$), 1.20 (3 H, d, J = 7.0, $C_{12}CH_3$).

Compound 15a: light foam; HPLC (54:36:10 CH_3CN–MeOH–H_2O, 1.5 mL/min) t_R 13.5 min (99%); UV (MeOH) λ_{max} 243 nm (ε 29300); HRMS m/e found 702.4330 (M^+), calcd for $C_{40}H_{63}FO_7Si$ 702.4326; MS, m/e 702 (M^+), 460 (retro-Diels–Alder product); 200-MHz ^1H NMR ($CDCl_3$) δ 4.41 (1 H, dd, J = 10, 48 Hz, $C_{13\alpha}H$), 4.44 (1 H, br m, C_5H), 4.05 (1 H, s, C_7OH), 3.82 (1 H, d, J = 6.0 Hz, C_6H), 3.36 (1 H, q, J = 2.2 Hz, C_2H), 2.60 (1 H, m, $C_{12}H$), 1.14 (3 H, d, J = 7.5, $C_{12}CH_3$). Irradiation of $C_{12}H$ at δ 2.60: δ 4.46 (1 H, d, J = 48 Hz, $C_{13\alpha}H$), 1.14 (3 H, s, $C_{12}CH_3$).

13-Deoxy-22,23-dihydro-13α-fluoroavermectin B_{1a} Aglycon (14b). Compound 14a (1.22 g) was deprotected according to general procedure A and purified by column chromatography on 150 g of silica gel with a 9:1 CH_2Cl_2–EtOAc solvent mixture to give 788 mg of 14b, which was freeze-dried from benzene: HPLC (51:34:15 CH_3CN–Me_3OH–H_2O, 1.0 mL/min) t_R 10.6 min (98%); UV (MeOH) λ_{max} 243 nm (ε 29750); HRMS m/e found 588.3492 (M^+), calcd for $C_{34}H_{49}FO_7$ 588.3462; 400-MHz ^1H NMR ($CDCl_3$) δ 4.72 (1 H, br d, J = 48 Hz, $C_{13\beta}H$), 4.30 (1 H, br t, J = 8 Hz, C_5H), 4.07 (1 H, s, C_7OH), 3.97 (1 H, d, J = 6 Hz, C_6H), 3.26 (1 H, q, J = 2 Hz, C_2H), 2.53 (1 H, m, $C_{12}H$), 2.31 (1 H, d, J = 8 Hz, C_5OH), 1.19 (3 H, d, J = 6 Hz, $C_{12}CH_3$).

13-Deoxy-22,23-dihydro-13β-fluoroavermectin B_{1a} Aglycon (15b). Compound 15a (500 mg) was deprotected according to general procedure A and purified by column chromatography on 50 g of silica gel with a 9:1 CH_2Cl_2–EtOAc solvent mixture to give 275 mg of 15b, which was freeze-dried from benzene: HPLC (51:34:15 CH_3CN–MeOH–H_2O, 1.0 mL/min) t_R 10.1 min (100%); UV (MeOH) λ_{max} 244 nm (ε 29600); HRMS m/e found 588.3475 (M^+), calcd for $C_{34}H_{49}FO_7$ 588.3462; 400-MHz ^1H NMR ($CDCl_3$) δ 4.41 (1 H, dd, J = 48, 10 Hz, $C_{13\alpha}H$), 4.29 (1 H, br t, J = 8 Hz, C_5H), 4.02 (1 H, s, C_7OH), 3.97 (1 H, d, J = 6 Hz, C_6H), 3.26 (1 H, m, C_2H), 2.60 (1 H, m, $C_{12}H$), 2.31 (1 H, d, J = 8 Hz, C_5OH), 1.16 (3 H, d, J = 6 Hz, $C_{12}CH_3$).

13-Deoxy-22,23-dihydro-13α-fluoroavermectin B_{1a} Aglycon (14b) and 13-Deoxy-22,23-dihydro-13β-fluoroavermectin B_{1a} Aglycon (15b) from Tosylate 8a. A solution of crude 8a (200 mg, 88% 8a + 12% 2a, 0.2 mmol of 8a) in 2.0 mL of THF–HF–pyridine reagent [mixture of THF–pyridine–(commercial hydrogen fluoride–pyridine, HF 70%, pyridine 30%, Aldrich) in a ratio 60:30:10 by volume] was held at room temperature for 72 h. The reaction mixture was poured onto cold, aqueous $NaHCO_3$ and extracted with CH_2Cl_2, and the extract was dried and concentrated in vacuo to 150 mg of crude product, which was first purified on a silica gel column (hexane–EtOAc, 93:7 to 80:20) to give 82 mg of product mixture: HPLC (85:15 MeOH–H_2O, 1.5 mL/min) t_R 5.66, 12.97, 15.50 min (23% 1b, 40% 14b + 15b, 27% 2b). Further separation by PTLC (SiO_2, hexane–EtOAc, 80:20) gave 14 mg of pure α-fluoride identical with authentic 14b by HPLC and mass and 300-MHz ^1H NMR spectra and 19 mg of a mixture of 2b and 15b (77% and 23%, respectively), in which 15b was identified through HPLC and mass and 300-MHz ^1H NMR spectra.

5-*O*-(*tert*-Butyldimethylsilyl)-22,23-dihydro-13-oxoavermectin B_{1a} Aglycon (16a). A solution of DMSO (68.6 mg, 62 μL, 0.88 mmol) in CH_2Cl_2 (0.4 mL) was added to a solution of oxalyl chloride (55 mg, 38.4 μL, 0.44 mmol) in CH_2Cl_2 (1.0 mL) which was stirred under N_2 at −60 °C. Two minutes later a solution of 1a (140 mg, 0.2 mmol) in CH_2Cl_2 (1.2 mL) was added dropwise through a syringe. Stirring was continued at −60 °C for 30 min, when triethylamine (203 mg, 280 μL, 2.0 mmol) was added. The cooling bath was removed, and the reaction mixture was stirred at ambient temperature for 45 min. Workup by addition of water, extraction with CH_2Cl_2, washing with water, drying, and concentration in vacuo gave a light foam. This was purified by preparative TLC (1.0-mm thickness, CH_2Cl_2–MeOH, 95:5) to give 80 mg of 16a (amorphous solid from benzene lyophilization): HPLC (95:5 MeOH–H_2O, 1.0 mL/min) t_R 9.23 min (99%); UV (MeOH) λ_{max} 232, sH 246 nm (ε 21400, 19300); HRMS m/e found 698.4215 (M^+), calcd for $C_{40}H_{62}O_8Si$ 698.4214; 200-MHz ^1H NMR ($CDCl_3$) δ 6.24 (1 H, t, J = 8 Hz, $C_{15}H$), 6.08 (1 H, dd, J = 15, 10 Hz, $C_{10}H$), 5.86 (1 H, dt, J = 10, 2.5 Hz, C_9H), 5.45 (1 H, dd, J = 15, 10 Hz, $C_{11}H$), 5.36 (1 H, q, J = 1 Hz, C_3H), 5.31 (1 H, m, $C_{19}H$), 4.77 (1 H, dd, J = 15, 2 Hz, $C_{8a}H$), 4.64 (1 H, dd, J = 15, 2 Hz, $C_{8a}H$), 4.47 (1 H, br m, C_5H), 4.37 (1 H, s, C_7OH), 3.87 (1 H, d, J = 6 Hz, C_6H), 3.45 (1 H, q, J = 2 Hz, C_2H), 3.20 (1 H, d, J = 7.5 Hz, $C_{25}H$), 2.58 (1 H, m, $C_{12}H$), 1.83 (3 H, s, C_4CH_3), 1.53 (3 H, s, $C_{14}CH_3$), 1.19 (3 H, d, J = 6.5, $C_{12}CH_3$).

5-*O*-(*tert*-Butyldimethylsilyl)-22,23-dihydroavermectin B_{1a} Aglycon (1a) from 16a. A solution of 16a (17.5 mg, 0.025 mmol) and $NaBH_4$ (10 mg, 0.26 mmol) in MeOH (2 mL) was stirred at 20 °C for 30 min. The reaction mixture was poured onto aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried, and concentrated. TLC (SiO_2, 6:4 petroleum ether–ether) and HPLC [95:5 MeOH–H_2O, 1.0 mL/min, t_R 8.33 min (97%)] showed only 1a and no 13-epimer 7a. Purification by PTLC (SiO_2, 97.5:2.5 CH_2Cl_2–EtOAc) gave 15 mg of amorphous product, which was by TLC, HPLC, and 200-MHz ^1H NMR identical with 1a.

22,23-Dihydro-13-oxoavermectin B_{1a} Aglycon (16b). Reaction of 16a (100 mg) according to general procedure A and purification by preparative TLC (0.5 mm of SiO_2, CH_2Cl_2–MeOH, 95:5) gave 62 mg of 16b (amorphous solid from benzene lyophilization): HPLC (80:20 MeOH–H_2O, 1.5 mL/min) t_R 10.50 min (100:); UV (MeOH) λ_{max} 230, sh 244 nm (ε 23400, 20100); HRMS m/e found 584.3342 (M^+), calcd for $C_{34}H_{48}O_8$ 584.3349; MS, m/e 584 (M^+), 456, 323, 305, 223, 195, 171; 200-MHz ^1H NMR ($CDCl_3$) in close agreement with 16a except for the absence of *tert*-butyldimethylsilyl peaks and the expected minor shifts for C_3H, C_5H, C_6H, $C_{8a}CH_2$ peaks (δ 5.45, 4.34, 4.01, 4.74, respectively).

5-Oxo-22,23-dihydroavermectin B_{1a} Aglycon. A solution of 100 mg of 1b in 10 mL of ether and 250 mg of MnO_2 was stirred at room temperature for 3 h, when an additional 250-mg quantity of MnO_2 was added. After a further 1 h of stirring, the reaction was complete (TLC SiO_2, CH_2Cl_2–EtOAc, 85:15, single spot, R_f 0.80, starting material R_f 0.35). The product was isolated by centrifugation, washing with ether, washing of the solution with aqueous $NaHCO_3$ and H_2O, drying, and concentration to 68 mg of yellow foam, and purification by PTLC gave 57 mg: HRMS m/e (M^+) calcd for $C_{34}H_{48}O_8$ 584.3348 (M^+), found 584.3347; UV λ_{max} 241 nm (ε 26800); 400-MHz ^1H NMR ($CDCl_3$) δ 6.57 (1 H, m, C_3H), 4.01 (1 H, s, C_7OH), 3.99 (1 H, br s, $C_{13}H$), 3.53 (1 H, quintet, J = 2.5 Hz, C_2H), 1.86 (3 H, br s, C_4CH_3), 1.15 (3 H, d, J = 7 Hz, $C_{12}CH_3$).

5-*O*-(*tert*-Butyldimethylsilyl)-13-deoxy-22,23-dihydro-13-(methoxyimino)avermectin B_{1a} Aglycon (17a), Geometric Isomers A and B. A solution of 16a (247 mg, 0.35 mmol), methoxylamine hydrochloride (293 mg, 3.5 mmol), and 2.0 mL of pyridine in 12 mL of absolute EtOH was stirred at reflux under N_2 for 4.5 h and then concentrated in vacuo. The residue was taken up in CH_2Cl_2 and washed with aqueous $NaHCO_3$. The CH_2Cl_2 layer was separated, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by PTLC on silica gel (15:85 Et_2O–petroleum ether) by using multiple development to furnish 140 mg of isomer mixture A and B of 17a and 32.6 mg of pure isomer B of 17a. The 140-mg mixture was separated by PTLC on silica gel (10:90 Et_2O–petroleum ether, multiple development), providing 67 mg of 17a, isomer A: HPLC (90:10 MeOH–H_2O, 1.5 mL/min) t_R 19.83 (99%); MS, m/e 727 (M^+), 670, 485, 454;

200-MHz ^{1}H NMR ($CDCl_3$) δ 5.37 (1 H, br s, C_3H), 446 (1 H, m, C_5H), 4.09 (1 H, s, C_7OH), 3.84 (3 H, s, $NOCH_3$), 3.41 (1 H, nm, C_2H), 2.45 (1 H, m, $C_{12}H$), 1.22 (3 H, d, J = 6.5 Hz, $C_{12}CH_3$). Anal. ($C_{41}H_{65}O_8NSi$) C, H, N.

Compound **17a**, isomer B: HPLC (90:10 MeOH–H_2O, 1.5 mL/min) t_R 21.10 (98%); MS, m/e 727 (M^+), 696, 670, 485, 454; 200-MHz ^{1}H NMR ($CDCl_3$) δ 5.40 (1 H, br s, C_3H), 4.46 (1 H, m, C_5H), 4.28 (1 H, s, C_7OH), 3.90 (3 H, s, $NOCH_3$), 3.84 (1 H, d, J = 5.5 Hz, C_6H), 3.40 (1 H, nm, C_2H), 2.37 (3 H, br m, $C_{12}H$ and $C_{16}H_2$), 1.31 (3 H, d, J = 7.0 Hz, $C_{12}CH_3$).

13-Deoxy-22,23-dihydro-13-(methoxyimino)avermectin B_{1a} Aglycon (17b), Isomer A. Compound **17a**, isomer A (63 mg), was deblocked according to general procedure A, purified by PTLC on silica gel (CH_2Cl_2–MeOH–H_2O, 98.5:1.5:0.15) by using multiple development, and lyophilized from benzene, furnishing 31 mg of **17b**, isomer A: HPLC (85:15 MeOH–H_2O, 1.5 mL/min) t_R 10.07 min (97%); UV (MeOH) λ_{max} 245 nm (ϵ 30 300); HRMS m/e found 613.3618 (M^+), calcd for $C_{35}H_{51}O_8N$ 613.3614; MS, m/e 613 (M^+) 485, 454; 200-MHz ^{1}H NMR ($CDCl_3$) δ 4.34 (1 H, m, C_5H), 4.05 (1 H, s, C_7OH), 4.01 (1 H, d, J = 6.2 Hz, C_6H), 3.85 (3 H, s, $C_{13}NOCH_3$), 3.32 (1 H, q, J = 2.2, C_2H), 2.46 (1 H, br m, $C_{12}H$), 1.22 (3 H, d, J = 6.5 Hz, $C_{12}CH_3$). Anal. ($C_{35}H_{51}O_8N\cdot 0.5C_6H_6$) C, H, N.

13-Deoxy-22,23-dihydro-13-(methoxyimino)avermectin B_{1a} Aglycon (17b), Isomer B. Compound **17a**, isomer B (32 mg), was deblocked according to general procedure A, purified by PTLC on silica gel (CH_2Cl_2–MeOH, 98:2) by using multiple development, and lyophilized from benzene, providing 28 mg of **17b**, isomer B: HPLC (85:15 MeOH–H_2O, 1.5 mL/min) t_R 10.17 min (99%); UV (MeOH) λ_{max} 246 nm (ϵ 30 300); HRMS m/e found 613.3610 (M^+), calcd for $C_{35}H_{51}O_8N$ 613.3614; MS, m/e 613 (M^+) 485, 454; 200-MHz ^{1}H NMR ($CDCl_3$) δ 4.32 (1 H, m, C_5H), 4.11 (1 H, s, C_7OH), 3.98 (1 H, d, J = 6.3 Hz, C_6H), 3.91 (3 H, s, $NOCH_3$), 3.30 (1 H, q, J = 2.2 Hz, C_2H), 2.38 (3 H, br m, $C_{12}H$ and $C_{16}H_2$), 1.46 (3 H, d, J = 7.0 Hz, $C_{12}CH_3$). Anal. ($C_{35}H_{51}O_8N\cdot C_6H_6$) C, H, N.

13α-Amino-5-*O*-(*tert*-butyldimethylsilyl)-13-deoxy-22,23-dihydroavermectin B_{1a} Aglycon (18a). Compound **16a** (669 mg, 1.0 mmol), ammonium acetate (771 mg, 10. mmol), and powdered 3A molecular sieves (700 mg) were stirred in dry MeOH (15 mL) at 21 °C under N_2 for 4 h. Sodium cyanoborohydride (57 mg, 0.91 mmol) dissolved in 2.5 mL of dry MeOH was added and stirring continued for 48 h. The mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to 647 mg of yellow foam. The residue was chromatographed on a column of silica gel (99:1.0:0.1 CH_2Cl_2–MeOH–H_2O), furnishing 217 mg of **18a**: HPLC (99.5:0.5 MeOH–H_2O, 1.5 mL/min) t_R 14.27 min (95%); UV (MeOH) λ_{max} 244 nm (ϵ 28 000); MS, m/e 699 (M^+), 681, 642, 624, 306; 200-MHz ^{1}H NMR ($CDCl_3$) δ 4.42 (1 H, br s, C_5H), 4.12 (1 H, s, C_7OH), 3.82 (1 H, d, J = 6.0 Hz, C_6H), 3.35 (1 H, m, C_2H), 3.31 (1 H, br s, $C_{13}H$), 2.58 (1 H, br m, $C_{12}H$), 1.12 (3 H, d, J = 7.0 Hz, $C_{12}CH_3$). Anal. ($C_{40}H_{65}NO_7Si$) C, H, N.

13α-Amino-13-deoxy-22,23-dihydroavermectin B_{1a} Aglycon (18b). Compound **18a** (40 mg) was deblocked according to general procedure A and was chromatographed on a column of silica gel (95:5:0.5 CH_2Cl_2–MeOH–H_2O), furnishing 11 mg of **18b**: HPLC (85:15 MeOH–H_2O, 1.5 mL/min) t_R 14.2 (97%); UV (MeOH) λ_{max} 245 nm (ϵ 26 300); HRMS m/e found 585.3677 (M^+), calcd for $C_{34}H_{51}NO_7$ 585.3666; MS, m/e 585 (M^+), 567, 550, 528, 306; 200-MHz ^{1}H NMR ($CDCl_3$) δ 4.69 (2 H, br s, $C_{8a}CH_2$), 4.31 (1 H, d, J = 6.0 Hz, C_5H), 3.98 (1 H, d, J = 6.0 Hz, C_6H), 3.33 (1 H, br s, $C_{13}H$), 3.28 (1 H, m, C_2H), 2.60 (1 H, br m, $C_{12}H$), 1.13 (3 H, d, J = 6.5 Hz, $C_{12}CH_3$). Anal. ($C_{34}H_{51}NO_7\cdot 0.5H_2O$) C, H, N.

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Registry No. **1a**, 73162-96-6; **1b**, 73162-95-5; **2a**, 73162-97-7; **2b**, 117858-36-3; **3b**, 73162-99-9; **4a**, 103967-89-1; **4b**, 117755-67-6; **5a** (R_2 = MeNH), 117755-68-7; **5a** (R_2 = $N(CH_3)COCH_3$), 117755-69-8; **5b**, 117755-70-1; **6a**, 117755-71-2; **6b**, 117755-72-3; **7a**, 104013-32-3; **7b**, 113625-74-4; **7c**, 101006-85-3; **8a**, 117755-73-4; **9a**, 117755-74-5; **9b**, 117774-74-0; **10a**, 117755-75-6; **10b**, 117774-75-1; **11a**, 103967-61-9; **11b**, 103968-19-0; **12a**, 104013-34-5; **12b**, 105814-37-7; **13a**, 104420-32-8; **13b**, 104370-25-4; **14a**, 104420-35-1; **14b**, 104370-27-6; **15a**, 104370-26-5; **15b**, 104420-36-2; **16a**, 103465-41-4; **16b**, 103465-43-6; **17a** (*E*-imino isomer), 117858-37-4; **17a** (*Z*-imino isomer), 117859-00-4; **17b** (*E*-imino isomer), 103465-53-8; **17b** (*Z*-imino isomer), 103531-72-2; **17b** $\Delta^{13,14}$-15-(4-morpholinyl) derivative, 117755-76-7; **18a**, 117858-38-5; **18b**, 117859-01-5; 5-oxo-22,23-dihydroavermectin B_{1a} aglycon, 105457-31-6.