anes/ethyl acetate (500 mL). The latter two fractions were separately evaporated under reduced pressure, and the residual materials were purified as described below to provide the three thermal transformation products **6a**, **7a**, and **8a**.

2-(4′-Chlorophenyl)-5,11-dihydropyrido[3,2-*c*][1,5]benzothiazepine (6a) was obtained as a pale red solid (0.05 g, 1%) upon column chromatography (80% methylene chloride/hexanes as eluent); mp 154–156 °C: R_f = 0.64 in methylene chloride; ^{1}H NMR ($CDCl_3$) δ 7.93–7.90 (m, 2 H), 7.53 (bs, 1 H), 7.44–7.41 (m, 2 H), 7.39–7.36 (m, 1 H), 7.32 (d, J = 7.7 Hz, 1 H), 7.24–7.18 (m, 1 H), 7.09 (d, J = 7.7 Hz, 1 H), 6.98–6.95 (m, 1 H), 6.91–6.86 (m, 1 H), 3.90 (s, 2 H); HRMS calcd for $C_{18}H_{13}N_2SCl$ m/z 324.0488, found m/z 324.0473.

2-(4′-Chlorophenyl)-4-methyl-10*H*-pyrido[3,2-*b*][1,4]benzothiazine (7a). The methylene chloride fraction obtained from the above reaction was sequentially evaporated under reduced pressure to afford **7a** as orange needles (1.66 g). The residue remaining after a third crop of crystals was obtained was purified by column chromatography (80% methylene chloride/hexanes eluent) to afford 0.14 g of additional product (39% total yield), mp 198–199 °C: R_f = 0.60 in methylene chloride; ^{1}H NMR ($CDCl_3$) δ 7.84–7.79 (m, 2 H), 7.40–7.36 (m, 2 H), 7.02–6.96 (m, 3 H), 6.85–6.79 (m, 1 H), 6.55 (bs, 1 H), 6.52 (d, J = 7.8 Hz, 1 H), 2.23 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 152.99, 152.10, 144.86, 140.90, 137.63, 135.22, 129.37, 128.30, 128.17, 127.05, 123.51, 117.28, 117.08, 115.37, 113.04, 20.00; HRMS calcd for $C_{18}H_{13}N_2SCl$ m/z 324.0488, found m/z 324.0482. Anal. Calcd for $C_{18}H_{13}N_2SCl$: C, 66.56; H, 4.03; N, 8.62; S, 9.87; Cl, 10.91. Found: C, 66.85; H, 3.90; N, 8.51; S, 9.89; Cl, 11.08.

3-(2*H*-1-Benzothiopyran-8-ylamino)-5-(4′-chlorophenyl)-1,2,4-triazine (8a). Method A. The 1:1 hexanes/ethyl acetate fraction was evaporated under reduced pressure to afford **8a** in a trace amount (R_f = 0.58 in 1:1 hexanes/ethyl acetate). The spectral and physical properties of this compound were identical with those of **8a** prepared as described below under method B.

Method B. A stirred suspension of **4a** (0.04 g, 0.11 mmol) in bromobenzene (8 mL) was heated at reflux under nitrogen for 75.5 h. After this period, the reaction mixture was cooled to room temperature and filtered through a silica gel pad, eluting successively with hexanes (200 mL), methylene chloride (200 mL), and ethyl acetate (200 mL). The methylene chloride fraction was evaporated under reduced pressure, and the residue was purified by preparative thin layer chromatography (1:1 hexanes/ethyl acetate as eluent) to afford 0.01 g of an orange solid identified by ^{1}H NMR ($CDCl_3$) as a mixture of the 1,5-benzothiazepine **6a** and the 1,4-benzothiazine **7a** (5% and 20% yield, respectively, based upon relative NMR peak integrations). The spectral properties of these materials were identical with those of **6a** and **7a** prepared as described above.

The ethyl acetate fraction was evaporated under reduced pressure, and the residual oil was purified twice by preparative thin layer chromatography (1:1 hexanes/ethyl acetate as eluent) to afford 3-(2*H*-1-benzothiopyran-8-ylamino)-5-(4′-chlorophenyl)-1,2,4-triazine (**8a**) (0.02 g, 50%) as a yellow solid, mp 164–166 °C: IR (KBr) 3290, 1585, 1540, 1520, 1460, 1420, 1300, 1280, 1090, 1060, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.21 (s, 1 H), 8.12–8.09 (m, 3 H), 7.59–7.53 (m, 3 H), 7.21 (t, J = 7.8 Hz, 1 H), 6.93 (d, J = 7.3 Hz, 1 H), 6.59 (dt, J_1 = 10.1 Hz, J_2 = 1.3 Hz, 1 H), 6.07–6.00 (m, 1 H), 3.50 (dd, J_1 = 5.3 Hz, J_2 = 1.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 160.45, 154.75, 138.97, 138.80, 135.17, 133.24, 132.34, 130.10, 129.69, 128.95, 125.58, 123.79, 122.57, 122.04, 121.44, 24.94; HRMS calcd for $C_{18}H_{13}N_4SCl$ m/z 352.0549, found m/z 352.0537.

Thermal Transformations of 5-(4′-Methoxyphenyl)-3-[[2′-(2-propynylthio)phenyl]amino]-1,2,4-triazine (4b). A stirred suspension of **4b** (0.40 g, 1.15 mmol) in bromobenzene (10 mL) was heated at reflux under nitrogen for 67.5 h and filtered through a silica gel pad, with successive elution with hexanes (250 mL), methylene chloride (600 mL), and 1:1 hexanes/ethyl acetate (400 mL). The latter two fractions were separately evaporated under reduced pressure, and the residual materials were purified as described below to provide the three thermal transformation products **6b**, **7b**, and **8b**.

2-(4′-Methoxyphenyl)-5,11-dihydropyrido[3,2-*c*][1,5]benzothiazepine (6b) was obtained as a pale yellow solid (0.01 g, 3%), mp 149–151 °C, upon column chromatography (methylene chloride eluent, R_f = 0.16 in methylene chloride): ^{1}H NMR ($CDCl_3$) δ 7.93–7.90 (m, 2 H), 7.52 (bs, 1 H), 7.38–7.35 (m, 1 H), 7.30 (d, J = 7.7 Hz, 1 H), 7.23–7.18 (m, 1 H), 7.07 (d, J = 7.6 Hz, 1 H), 7.01–6.95 (m, 3 H), 6.90–6.84 (m, 1 H), 3.91 (s, 2 H), 3.87 (s, 3 H); HRMS calcd for $C_{19}H_{16}N_2OS$ m/z 320.0983, found m/z 320.0975.

2-(4′-Methoxyphenyl)-4-methyl-10*H*-pyrido[3,2-*b*][1,4]benzothiazine (7b). The methylene chloride fraction was evaporated under reduced pressure, and the residual orange solid was purified by column chromatography (methylene chloride eluent) to provide **7b** (0.08 g, 22%) as a pale orange solid, mp 167.5–169 °C: R_f = 0.15 in methylene chloride; ^{1}H NMR ($CDCl_3$) δ 7.84–7.81 (m, 2 H), 7.01–6.93 (m, 5 H), 6.84–6.78 (m, 1 H), 6.61 (bs, 1 H), 6.52–6.49 (m, 1 H), 3.85 (s, 3 H), 2.23 (s, 3 H); HRMS calcd for $C_{19}H_{16}N_2OS$ m/z 320.0983, found m/z 320.0976.

3-(2*H*-1-Benzothiopyran-8-ylamino)-5-(4′-methoxyphenyl)-1,2,4-triazine (8b). The 1:1 hexanes/ethyl acetate fraction was evaporated under reduced pressure, and the residual dark resin was purified by column chromatography (1:1 hexanes/ethyl acetate eluent) to provide **8b** as a yellow solid (0.07 g, 18%), mp 143.5–145.5 °C: R_f = 0.41 in 1:1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 9.16 (s, 1 H), 8.15–8.09 (m, 3 H), 7.50 (bs, 1 H), 7.18 (t, J = 7.9 Hz, 1 H), 7.05–7.02 (m, 2 H), 6.88 (d, J = 7.4 Hz, 1 H), 6.58 (dd, J_1 = 8.6 Hz, J_2 = 1.4 Hz, 1 H), 6.05–5.98 (m, 1 H), 3.90 (s, 3 H), 3.48 (dd, J_1 = 5.1 Hz, J_2 = 1.2 Hz, 2 H); HRMS calcd for $C_{19}H_{16}N_4OS$ m/z 348.1045, found m/z 348.1039.

Registry No. **1a**, 105783-78-6; **1b**, 114954-25-5; **2a**, 118632-00-1; **2b**, 118632-01-2; **3a**, 118632-02-3; **3b**, 118632-03-4; **4a**, 118632-04-5; **4b**, 118632-05-6; **5**, 118632-06-7; **6a**, 118632-07-8; **6b**, 118632-08-9; **7a**, 118632-09-0; **7b**, 118657-03-7; **8a**, 118632-10-3; **8b**, 118632-11-4; 2-aminothiophenol, 137-07-5; propargyl bromide, 106-96-7.

N-Bromoacetamide as a Selective Reagent for the Functionalization of the 10,11 Double Bond of Avermectin B1a

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The avermectins and related milbemycins are a class of extremely potent anthelminthic and pesticidal agents.[1] In addition to being the focus of total synthetic efforts,[2] these unique macrolactonic structures are the target of transformation and derivatization with the goals of improving and/or shifting the spectrum of activity. One important advance from these efforts has been the selective hydrogenation of the 22,23 double bond of avermectin B1a (1) with Wilkinson's catalyst to produce ivermectin (3).[3] Since that discovery we have continued to explore the selective functionalization of the other double bonds. In particular, modification of the 8,9 or 10,11 double bonds became of interest since it appears that the 8,9,10,11-diene chromophore is responsible for the isomerization and photodecomposition of the avermectins.[4] Our investiga-

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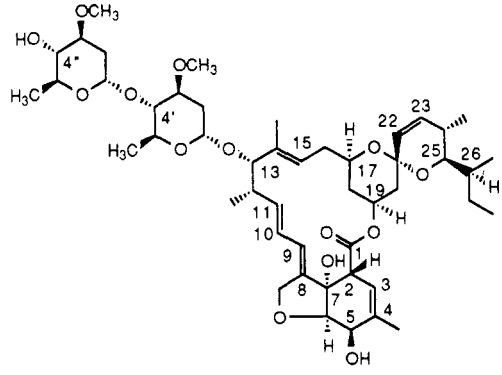
AVERMECTIN B_{1a}



1

2 10,11-dihydro-**1**
3 22,23-dihydro-**1**
4 10,11,22,23-tetrahydro-**1**
5 3,4,10,11,22,23-hexahydro-**1**
6 3,4,8,9,10,11,22,23-octahydro-**1**

tion of the hydrogenation of avermectin B1a (**1**) with palladium supported on carbon, using varying amounts of hydrogen, yielded a number of reduction products, predominantly the 10,11,22,23-tetrahydro derivative **4**, but only very small amounts of the desired 10,11-dihydroavermectin B1a (**2**) (see Experimental Section). We therefore investigated electrophilic reagents in an attempt to differentiate the reactivity of the olefins. We reasoned that the 22,23-olefin is more electron-deficient than the 8,9,10,11-diene due to the former's proximity to the electron-demanding spiroketal moiety. The only selective reaction of the 8,9 double bond of the diene reported to date is epoxidation with peracids[5] or *tert*-butyl hydroperoxide, under Sharpless conditions,[6] making use of the allylic C-7 hydroxy group to obtain regiospecificity.

Results and Discussion

When a solution of avermectin B1a (**1**) in ethanol was hydrogenated in the presence of 5% palladium supported on carbon and the hydrogen uptake was monitored until 0.5 equiv of hydrogen was absorbed, the product analysis (HPLC, 210 nm, UV detection) showed a ratio of 7:2:1 of avermectin B1a (**1**):10,11-dihydroavermectin B1a (**2**):22,23-dihydroavermectin B1 (**3**, ivermectin). Further hydrogen uptake afforded a mixture with the 10,11,22,23-tetrahydro- (**4**) and 3,4,10,11,22,23-hexahydroavermectin B1a (**5**) in a ratio of 2:1, respectively, as the major products. High pressure hydrogenation resulted in a mixture of 3,4,10,11,22,23-hexahydro- (**5**) and 3,4,8,9,10,11,22,23-octahydroavermectin B1a (**6**, only one of several possible stereoisomers isolated), leading one to assign a relative hydrogenation reactivity order of 10,11 $\approx$ 22,23 > 3,4 > 8,9 $\gg$ 14,15[7] double bonds for Pd/C.

A more fruitful approach to the selective saturation of the 10,11 double bond was found by use of an electrophilic reagent that could differentiate the electron-rich diene from the other double bonds. It was found that hypobromous acid, generated from *N*-bromoacetamide in aqueous acetone, represents such a reagent with the required regiospecificity. Treatment of avermectin B1a (**1**) with this reagent at 20 °C for 1 h resulted in the formation of a bromohydrin at the 10,11 position exclusively (Scheme I). This reaction proceeds equally well on **1** that has been protected at the 5- and/or 4″-hydroxyl positions, to afford the correspondly protected bromohydrins **7**. These bromohydrins are readily reduced with tributyltin hydride to the 10-hydroxyavermectin B1a derivatives **8**. Besides complete selectivity for the 10,11 double bond, only one of the possible regio- and stereoisomers was isolated from the reaction mixture. The 11-bromo-10-hydroxy substitution could be readily deduced from the ^{1}H NMR spectra of bromohydrin **7** and its halogen-free reduction product **8**. This conforms with the proposed reaction mechanism[8] favoring the more stable 11-bromo-8,9-allylic 10-carbonium ion as intermediate. The stereochemistry at the new chiral centers is yet unknown. In order to allow further modifications and especially the deoxygenation of the newly formed 10-hydroxy analogue **8** in the presence of the 4″-, 5-, and 7-hydroxy groups, we investigated its relative reactivity toward silylating reagents. We discovered that the 10-hydroxyl position is rather hindered, since reaction of **8** with trimethylsilyl chloride resulted in silylation first at the 5- and then at the 4″-position. However, since the 10-position is the more reactive allylic center, after selectively silylating the other secondary allylic 5-hydroxyl by *tert*-butyldimethylsilyl chloride one is able to react the 10-hydroxyl in the presence of the free 4″- and 7-hydroxyls with (*N*,*N*-diethylamino)sulfur trifluoride[9] (DAST) and dichlorotriphenylphosphorane/triethylamine to produce the 10-fluoro- and 10-chloroavermectin B1 derivatives **10a** and **11**, respectively (Scheme II). In the chlorination reaction some allylic rearrangement product is also obtained, as apparent from the NMR spectrum of the unstable product mixture **11**. Reduction of this mixture with tributyltin hydride yields the 8,11-dihydro isomer **12** containing a 9,10 double bond in addition to the desired 10,11-dihydroavermectin B1a (**2**) as the major product. Only one of the two possible epimeric fluoro derivatives was observed. Thus, through this indirect route, we have been able to effect the selective hydrogenation and functionalization of the 10,11 double bond of avermectin B1a. The biological activities of the new compounds will be reported elsewhere.

Experimental Section

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 137 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian XL-300 spectrometer. Mass spectra were recorded on Varian Mat Bremen 731 and Mat 212 Finnagin spectrometers. Flash column chromatography was carried out on Merck silica gel 60, 230–400 mesh. Thin-layer chromatography (TLC) was performed on Analtech silica gel GF plates, visualized by UV fluorescence and staining with phosphomolybdic acid–ceric sulfate. All solvents (ether, tetrahydrofuran (THF), and toluene) were distilled under nitrogen from sodium benzophenone ketyl before use. Dry avermectin starting materials were obtained by drying a solution of the avermectin derivative in dichloromethane over anhydrous magnesium sulfate, filtration, and evaporation in vacuo overnight under high vacuum. High performance liquid chromatography (HPLC) was performed on the Waters PrepLC 500A for preparative separations utilizing two PrepPAK-500/silica cartridges. Analytical HPLC utilized a Whatman Partisil 10 ODS-3 C_{18} reverse phase column and UV detection set at 254 or 210 nm while preparative reverse phase separations were achieved

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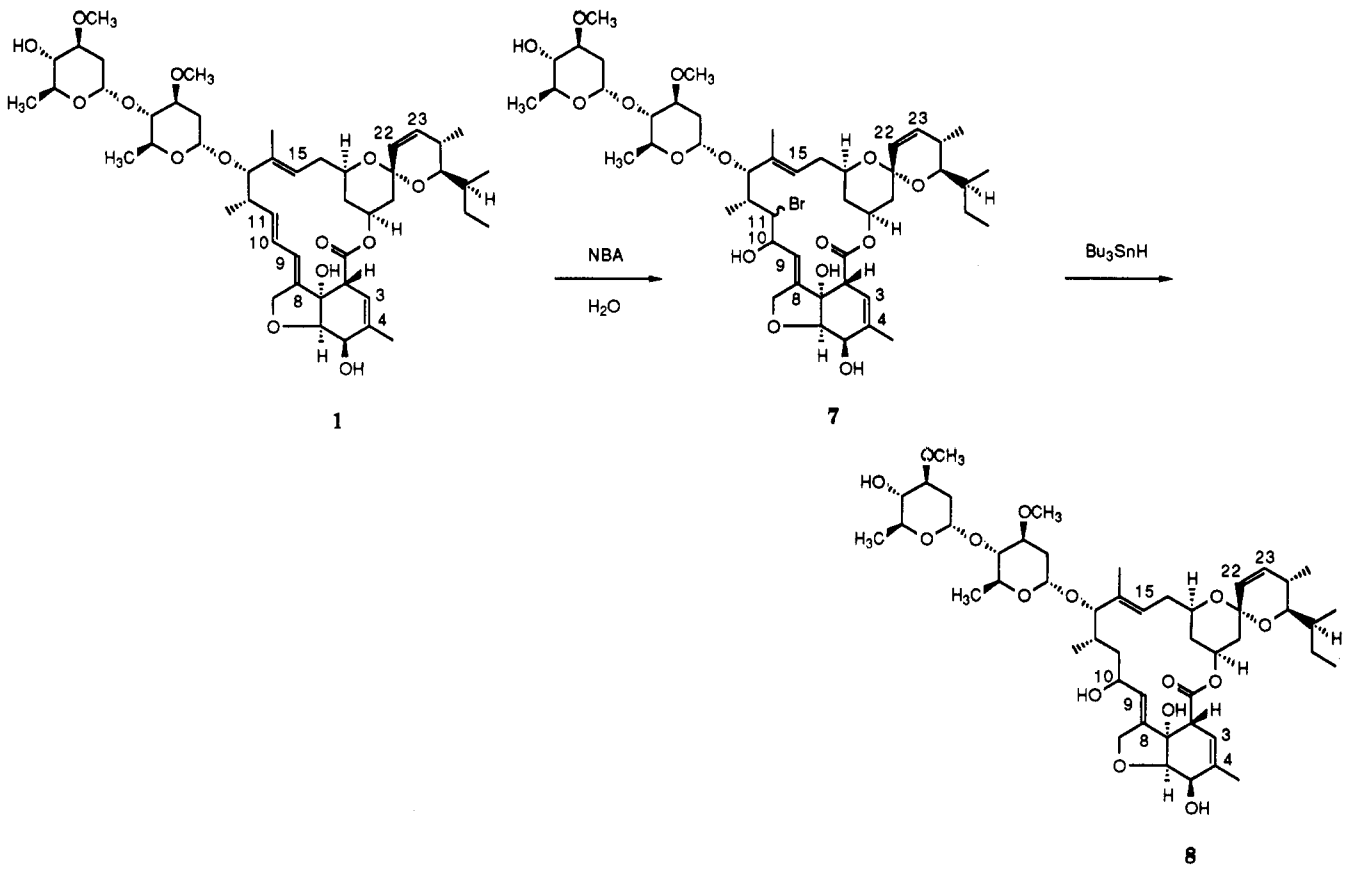
(9) While it was possible to prepare the 10-fluoro product starting with the unprotected 4″-hydroxy B_1 derivative, we chose to start with the protected 4″-OTMS compound since the overall yield is better.

Scheme I



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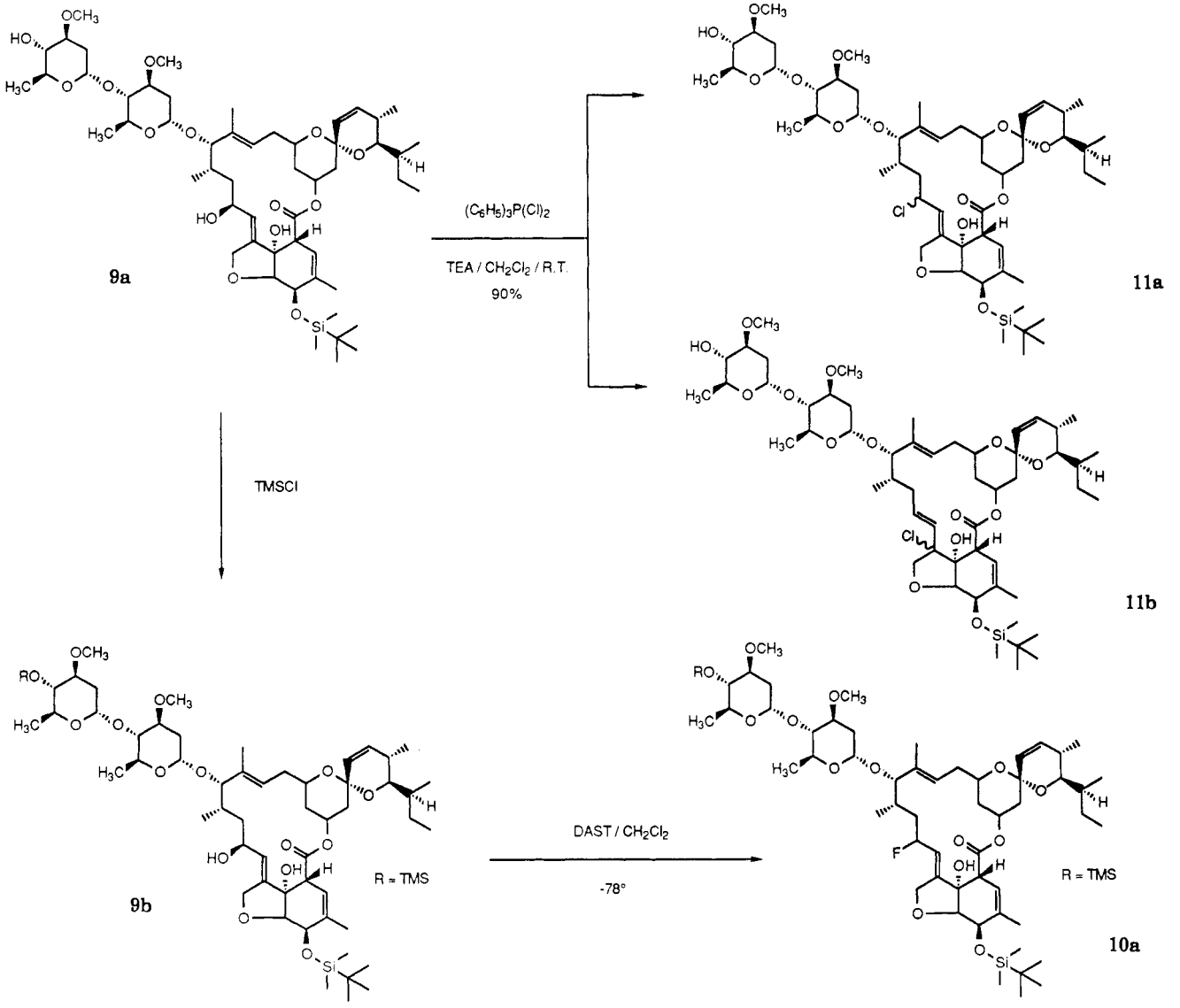
on a Whatman Partisil M20 10/50 ODS-3 column. All starting materials were obtained from Aldrich Chemical Company unless otherwise specified.

Hydrogenation of Avermectin B1 (1). A solution of 901 mg (1.1 mmol) of 1 in 50 mL of ethanol and 100 mg of 5% Pd supported on carbon is shaken under 20 psi of hydrogen at 29 °C until 0.5 mmol of hydrogen was taken up. The catalyst was removed by filtration and the reaction mixture was analyzed by reverse phase HPLC (80:20 v/v methanol/water, 1.5 mL/min flow rate). Product analysis indicated a ratio of 7:2:1- of 1:10,11-dihydroavermectin B1 (2)22,23-dihydroavermectin B1 (3) with retention times of 5.1, 5,6, and 7.9 min, respectively. Separation of these components was accomplished with the M20 column using the 80:20 methanol/water system collecting 20-mL fractions. The identities of the starting material and 22,23-dihydroavermectin B1 (3) were confirmed by comparison to authentic samples previously characterized.[3] The newly isolated product is 10,11-dihydroavermectin B1 (2), which has been synthesized by an independent route vide infra with the following characterization: ^{1}H NMR 0.89 (t, J = 7 Hz, 3 H), 0.91 (t, J = 6 Hz, 3 H), 1.25 (2 t, J = 8 Hz, 6 H), 1.4–1.7 (m), 1.51 (s, 3 H), 1.84 (s, 3 H), 1.86–2.20 (m, 4 H), 2.22 (d, J = 9 Hz, 1 H), 2.25–2.40 (m, 4 H), 2.46 (d, J = 2 Hz, 1 H), 3.15 (t, J = 9 Hz, 1 H), 3.22 (t, J = 9 Hz, 2 H), 3.41 (s, 3 H), 3.42 (s, 3 H), 3.44–3.52 (m, 2 H), 3.60 (m, 1 H), 3.80 (m, 2 H), 3.90–3.98 (m, 2 H), 3.94 (d, J = 6 Hz, 1 H), 4.28 (t, J = 7 Hz, 1 H), 4.54 (AB q, J = 16 Hz, 2 H), 4.71 (d, J = 4 Hz, 1 H), 5.0 (br d, 1 H), 5.07 (s, 1 H), 5.30 (dd, J = 3,10 Hz, 1 H), 5.31 (s, 1 H), 5.38 (d, J = 4 Hz, 1 H), 5.43 (m, 1 H), 5.56 (dd, J = 2, 10 Hz, 1 H), 5.77 (dd, J = 1.6, 10 Hz, 1 H); exact mass calcd for $C_{48}H_{74}O_{14}$ 874.5079, found 874.5065.

Hydrogenation of Ivermectin (22,23-Dihydroavermectin B1 (3)). A solution of 880 mg of 3 in 50 mL of ethanol and 200 mg of 5% Pd/C was shaken under 20 psi of hydrogen at 25 °C until 1 mmol of hydrogen was taken up. The catalyst was removed by filtration and the filtrate was analyzed by reverse phase HPLC (95:5 methanol/water, 1.5 mL/min, Waters Associates Radial-PAK μ-Bondapak C18 column). Product analysis indicated a ratio of 2:1 of 10,11,22,23-tetrahydroavermectin B1 (4):3,4,10,11,22,23-hexahydroavermectin B1 (5) (t_R of 5.56 and 6.32 min, respectively). These components were separated on a M20 reverse phase column using 90:10 methanol/water, collecting 20-mL fractions (210 nm UV detection) and characterized as follows. **10,11,22,23-Tetrahydroavermectin B1 (4):** ^{1}H NMR (400 MHz) 0.80 (d, J = 6 Hz, 3 H), 0.85 (d, J = 7 Hz, 3 H), 0.93 (t, J = 7.5 Hz, 3 H), 1.06 (d, J = 7 Hz, 3 H), 1.27 (t, J = 4 Hz, 3 H), 1.28 (d, J = 6 Hz, 3 H), 1.34–1.72 (m), 1.54 (s, 3H), 1.86 (s, 3H), 1.95 (m, 2 H), 2.04–2.46 (m), 2.18 (s, 1 H), 2.51 (br s, 1 H), 2.64 (s, 1 H), 3.17 (t, J = 9 Hz, 1 H), 3.22 (t, J = 3 Hz, 1 H), 3.23 (t, J = 9 Hz, 1 H), 3.42 (s, 3 H), 3.44 (s, 3 H), 3.40–3.53 (m, 2 H), 3.61 (m, 1 H), 3.78 (m, 3 H), 3.94 (br s, 1 H), 3.96 (d, J = 6 Hz, 1 H), 4.30 (t, J = 7 Hz, 1 H), 4.55 (t AB, J = 2 Hz, J_{AB} = 14 Hz, 2 H), 4.73 (d, J = 4 Hz, 1 H), 5.01 (br d, J = 10 Hz, 1 H), 5.14 (s, 1 H), 5.32 (m, 1 H), 5.34 (t, J = 3 Hz, 1 H), 5.39 (m, 1 H), 5.40 (d, J = 4 Hz, 1 H); MS M^+ 876, fragments, 714, 682, 588, 570, 307, 145, 113; exact mass calcd for $C_{48}H_{76}O_{14}$ 876.5235, found 876.5237. **3,4,10,11,22,23-Hexahydroavermectin B1 (5):** ^{1}H NMR 0.77 (d, J = 6 Hz, 3 H), 0.82 (d, J = 7 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H), 1.03 (d, J = 9 Hz, 3 H), 1.05 (d, J = 9 Hz, 3 H), 1.11 (d, J = 8 Hz, 2 H), 1.25 (t, J = 6.5 Hz, 8 H), 1.30–2.42 (m), 1.51 (s, 3 H), 2.48 (d, J = 2 Hz, 1 H), 3.15 (t, J = 9 Hz, 1 H), 3.21 (t, J = 9 Hz, 2 H), 3.41 (s, 3 H), 3.42 (s, 3 H), 3.40–3.64 (m, 3 H), 3.78 (m, 4 H), 3.91 (s, 1 H), 4.46 (AB q, J = 2 Hz, J_{AB} = 15 Hz, 2 H), 4.70 (d, J = 3 Hz, 1 H), 4.98 (d, J = 10 Hz, 1 H), 5.12 (s, 1 H), 5.20–5.40 (m, 2 H), 5.38 (d, J = 3 Hz, 1 H); exact mass calcd for $C_{48}H_{78}O_{14}$ 878.5392, found 878.5393.

3,4,8,9,10,11,22,23-Octahydroavermectin B1 (6). A solution of 1.0 g of ivermectin in 50 mL of ethanol and 200 mg of 5% Pd/C was shaken under 60 psi of hydrogen at 25 °C until 4 mmol of hydrogen was taken up. The catalyst was then removed by filtration and the filtrate was analyzed by reverse phase HPLC (95:5 methanol/water, 1.5 mL/min, Waters Associates Radial-PAK μ-Bondapak C18 columm) to indicate a ratio of 2:1 of 3,4,10,11,22,23-hexahydroavermectin B1 (5):3,4,8,9,10,11,22,23-octahydroavermectin B1 (6) (t_R 6.3 and 7.2 min, respectively). Preparative HPLC separation on a M20 column using 90:10 methanol/water afforded 230 mg of 5 and 130 mg of 3,4,8,9,10,11,22,23-octahydroavermectin B1 (6): ^{1}H NMR 0.77 (d, J = 5 Hz, 3 H), 0.81 (d, J = 7 Hz, 3 H), 0.89 (t, J = 7 Hz, 3

Scheme II



H), 1.01 (dd, J = 6, 7 Hz, 6 H), 1.24 (t, J = 6 Hz, 6 H), 1.31–1.80 (m), 1.52 (s, 3 H), 1.90 (dd, J = 5, 12 Hz, 1 H), 2.15 (m, 2 H), 2.34 (m, 5 H), 2.48 (s, 1 H), 3.15 (t, J = 6 Hz, 1 H), 3.21 (m, 2 H), 3.39 (s, 3 H), 3.40 (s, 3 H), 3.30–3.62 (m, 3 H), 3.76 (m, 3 H), 3.85 (d, J = 4 Hz, 1 H), 3.93 (s, 1 H), 4.12 (t, J = 9 Hz, 1 H), 4.70 (d, J = 3 Hz, 1 H), 5.03 (br d, J = 9 Hz, 1 H), 5.18 (s, 1 H), 5.36 (d, J = 3 Hz, 1 H), 5.36 (m, 1 H); exact mass calcd for $C_{48}H_{80}O_{14}$ 880.5548, found 880.5549.

11-Bromo-10,11-dihydro-10-hydroxyavermectin B1 (7). To a solution of 400 mg (0.46 mmol) of 1 in 9 mL of acetone and 1 mL of water at 20 °C was added 100 mg (0.72 mmol) of *N*-bromoacetamide in one portion. The reaction mixture was stirred, protected from light for 30 min, and analyzed by silica gel thin-layer chromatography (TLC). Elution of the TLC plate in 10% methanol–90% dichloromethane indicated a major product with an R_f of 0.6 (UV inactive). The reaction was stopped after 1 h by the addition of water and the cloudy mixture was extracted with dichloromethane. The extracts were combined and dried over magnesium sulfate. Evaporation of the solvent afforded 350 mg of a glassy solid. Purification of this mixture with four 1000-μm silica gel plates eluted in 10% methanol–90% dichloromethane afforded 210 mg of bromohydrin **7**: ^{1}H NMR (200 MHz) 0.84–1.02 (m, 9 H), 1.20 (d, J = 7 Hz, 3 H), 1.28 (d, J = 7 Hz, 3 H), 1.30 (d, J = 7 Hz, 3 H), 1.40–2.60 (m), 1.59 (s, 3 H), 1.88 (s, 3 H), 3.18 (t, J = 9 Hz, 1 H), 3.25 (t, J = 9 Hz, 1 H), 3.28 (sh m, 1 H), 3.42 (s, 3 H), 3.45 (s, 3 H), 3.32–4.20 (m), 3.96 (d, J = 6 Hz, 1 H), 4.04 (s, 2 H), 4.30 (br s, 2 H), 4.74 (br s, 1 H), 4.76 (AB q, J = 15 Hz, 2 H), 5.15 (br d, J = 6 Hz, 1 H), 5.39 (br s, 1 H), 5.41 (d, J = 3 Hz, 1 H), 5.44 (m, 1 H), 5.58 (dd, J = 3, 10 Hz, 1 H), 5.80 (dd, J = 2, 10 Hz, 1 H), 5.90 (d, J = 3 Hz, 1 H). This compound was not stable to storage and was not further characterized.

10,11-Dihydro-10-hydroxyavermectin B1 (8). A solution of 80 mg of **7** in 5 mL of toluene and 0.30 mL of tri-*n*-butyltin hydride was heated at 100 °C under nitrogen for 2.5 h. The reaction may be followed by reverse phase HPLC (85:15 methanol/water, 1.5 mL/min, 210 nm UV detection, Waters Associates Radial-PAK μ-Bondapak C18 column) in which the product 8 has a retention time of 7.7 min versus 6.8 min for bromohydrin **7**. The reaction mixture was evaporated to remove the solvent and the residual product and tin compounds were separated on a column of 50 g of silica gel, eluting with dichloromethane and then 10% methanol–90% dichloromethane. Final HPLC purification on a M20 reverse phase column (85:15 methanol/water) afforded 40 mg of pure **8** as a glass: ^{1}H NMR (400 MHz) 0.90 (d, J = 7 Hz, 3 H), 0.92 (d, J = 8 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H), 0.99 (q, J = 12 Hz, 1 H), 1.10 (d, J = 7 Hz, 3 H), 1.18 (d, J = 7 Hz, 1 H), 1.26 (d, J = 6 Hz, 3 H), 1.28 (d, J = 6.5 Hz, 3 H), 1.32 (m, 1 H), 1.40–1.66 (m), 1.53 (s, 3 H), 1.86 (s, 3 H), 2.0 (m, 3 H), 2.22 (sh, d, J = 10 Hz, 1 H), 2.22 (dd, J = 6, 12 Hz, 1 H), 2.28 (m, 1 H), 2.32 (d, J = 4 Hz, 1 H), 2.34–2.43 (m, 2 H), 2.52 (d, J = 2 Hz, 1 H), 3.17 (dt, J = 2, 9 Hz, 1 H), 3.24 (t, J = 9 Hz, 1 H), 3.25 (t, J = 3 Hz, 1 H), 3.42 (s, 3 H), 3.46 (s, 3 H),3.48 (m, 2 H), 3.61 (m, 1 H), 3.79 (m, 2 H), 3.90 (d, J = 6 Hz, 1 H), 3.98 (m, 1 H), 4.02 (br s, 1 H), 4.30 (m, 1 H), 4.41 (m, 1 H), 4.74 (d, J = 4 Hz, 1 H), 4.74 (dt, J = 3, 15 Hz, 1 H), 4.88 (dt, J = 3, 15 Hz, 1 H), 4.99 (d, J = 10 Hz, 1 H), 5.25 (s, 1 H), 5.30 (q, J = 2

Hz, 1 H), 5.33 (q, J = 2 Hz, 1 H), 5.40 (d, J = 4 Hz, 1 H), 5.44 (m, 1 H), 5.59 (dd, J = 3, 10 Hz, 1 H), 5.79 (dd, J = 2, 10 Hz, 1 H); exact mass calcd for $C_{41}H_{60}O_{11}$ (M - oleandrose - H_2O) 728.4136, found 728.4138.

5-*O*-(*tert*-Butyldimethylsilyl)-10,11-dihydro-10-hydroxyavermectin B1 (9a) and 4″-*O*-(Trimethylsilyl)-5-*O*-(*tert*-butyldimethylsilyl)-10,11-dihydro-10-hydroxyavermectin B1 (9b). To a solution of 2 g of dry **8** in 20 mL of dichloromethane were added 1 mL of distilled triethylamine, 1 g of *tert*-butyldimethylsilyl chloride, and 100 mg of 4-(*N*,*N*-dimethylamino)-pyridine. The mixture was stirred at 25 °C for 18 h. The product was isolated by flash column chromatography on silica gel with 1:1 ethyl acetate/hexane to yield 1 g of the 5-O-silylated product **9a** as a glassy solid: ^{1}H NMR 0.15 (s, 6 H), 0.90 (m, 16 H), 1.10 (d, J = 7 Hz, 3 H), 1.15 (d, J = 7 Hz, 1 H), 1.26 (t, J = 6 Hz, 9 H), 1.53 (s, 3 H), 1.55 (m, 7 H), 1.66 (s, 1 H), 1.78 (s, 3 H), 1.98 (m, 3 H), 2.15–2.40 (m, 6 H), 2.55 (sh d, J = 1 Hz, 1 H), 3.14 (t, J = 9 Hz, 1 H), 3.21 (t, J = 9 Hz, 1 H), 3.31 (d, J = 3 Hz, 1 H), 3.40 (s, 3 H), 3.42 (m, 3 H), 3.43 (s, 3 H), 3.58 (m, 1 H), 3.71 (d, J = 6 Hz, 1 H), 3.77 (m, 2 H), 3.94 (m, 1 H), 3.98 (br s, 1 H), 4.16 (br s, 1 H), 4.44 (br s, 1 H), 4.65 (d, J = 15 Hz, 1 H), 4.71 (d, J = 3 Hz, 1 H), 4.84 (d, J = 15 Hz, 1 H), 4.95 (d, J = 7 Hz, 1 H), 5.23 (s, 1 H), 5.26 (s, 1 H), 5.36 (s, 1 H), 5.37 (d, J = 3 Hz, 1 H), 5.40 (m, 1 H), 5.55 (dd, J = 3, 10 Hz, 1 H), 5.76 (d, J = 10 Hz, 1 H). To a solution of 1 g (1.0 mmol) of **9a** in 10 mL of dry dichloromethane were added 2 mL of molecular sieve dried *N*,*N*-dimethylformamide (DMF), 0.5 mL of distilled triethylamine, and 0.125 mL (1.0 mmol) of chlorotrimethylsilane. After 1 h at 25 °C, another 0.065 mL (0.5 mmol) of chlorotrimethylsilane was added. The reaction was analyzed after another 30 min by TLC (silica gel, 2:1 hexane/ethyl acetate, R_f(**9b**) = 0.6, R_f(**9a**) = 0.13), which indicated completion. The mixture was quenched with a saturated sodium bicarbonate solution and extracted with dichloromethane. The product was purified by flash column chromatography on silica gel (2:1 hexane/ethyl acetate) to afford 0.65 g of **9b** as a glassy solid: ^{1}H NMR 0.12 (s, 15 H), 0.80–1.00 (m, 19 H), 1.05 (d, J = 7 Hz, 3 H), 1.17 (d, J = 6 Hz, 3 H), 1.23 (d, J = 6 Hz, 3 H), 1.28 (m, 1 H), 1.30–1.70 (m, 4 H), 1.51 (s, 3 H), 1.78 (s, 3 H), 1.95 (m, 3 H), 2.12–2.40 (m, 5 H), 3.12 (t, J = 9 Hz, 1 H), 3.20 (t, J = 9 Hz, 1 H), 3.30–3.50 (m, 3 H), 3.38 (s, 3 H), 3.45 (s, 3 H), 3.56 (m, 1 H), 3.60–3.82 (m, 2 H), 3.72 (d, J = 4 Hz, 1 H), 3.96 (m, 1 H), 3.98 (br s, 1 H), 4.65 (dt, J = 2, 15 Hz, 1 H), 4.71 (d, J = 3 Hz, 1 H), 4.86 (dt, J = 2, 15 Hz, 1 H), 4.96 (d, J = 9 Hz, 1 H), 5.25 (d, J = 2 Hz, 1 H), 5.28 (d, J = 2 Hz, 1 H), 5.30 (d, J = 3 Hz, 1 H), 5.35 (s, 1 H), 5.40 (m, 1 H), 5.57 (dd, J = 3, 10 Hz, 1 H), 5.78 (dd, J = 2, 10 Hz, 1 H).

10-Fluoro-10,11-dihydroavermectin B1 (10b). To a solution of 840 mg (0.78 mmol) of **9b** in 10 mL of dichloromethane cooled to −78 °C was added 0.120 mL (0.91 mmol) of (*N*,*N*-diethylamino)sulfur trifluoride. The mixture was stirred at −78 °C for 2 h and TLC analysis showed no more progress in the conversion of starting material to product. The reaction was stopped by the addition of 2 mL of a 7% aqueous sodium carbonate solution, warming the mixture to room temperature, and extracting the product with dichloromethane. The product was isolated by flash column chromatography on silica gel (1:4 ethyl acetate/hexane) and further purified by reverse phase HPLC on the M20 column (91:9 methanol/water) to afford 314 mg of 4″-*O*-(trimethylsilyl)-5-*O*-(*tert*-butyldimethylsilyl)-10,11-dihydro-10-fluoroavermectin B1 (**10a**). Product **10a** was then dissolved in 5 mL of dry THF in a polypropylene flask and 15 mL of a solution of HF–pyridine (prepared by diluting 10 mL of commercially available pyridine–hydrogen fluoride complex in 60 mL of dry THF and 30 mL of distilled pyridine) was then added. After 20 h at room temperature, the reaction mixture was poured into a separatory funnel containing 200 mL of ice–water, carefully neutralized with sodium bicarbonate, and extracted with ether. The ethereal extracts were combined and dried over magnesium sulfate, filtered, and evaporated in vacuo to afford a solid, which was purified by preparative TLC (three 1-mm thick plates eluted in 1:3 hexane/ethyl acetate) to yield 200 mg of **10b** as a glassy solid: ^{1}H NMR 0.90 (m, 10 H), 1.20 (m, 10 H), 1.37–2.10 (m), 1.51 (s, 3 H), 1.81 (s, 3 H), 2.10–2.48 (m, 6 H), 2.50 (d, J = 2 Hz, 1 H), 3.17 (t, J = 9 Hz, 1 H), 3.21 (t, J = 9 Hz, 1 H), 3.21 (s, 1 H), 3.45 (s, 6 H), 3.30–3.70 (m, 3 H), 3.80 (m, 2 H), 3.90 (s, 1 H), 3.95 (m, 1 H), 3.98 (d, J = 6 Hz, 1 H), 4.30 (t, J = 6 Hz, 1 H), 4.60–4.90 (m, 4 H), 4.92 (s, 1 H), 5.03 (d, J = 12 Hz, 1 H), 5.34 (s, 1 H), 5.40 (d, J = 4 Hz, 1 H), 5.47 (m, 2 H), 5.58 (dd, J = 3, 10 Hz, 1 H), 5.79 (dd, J = 2, 10 Hz, 1 H); FAB MS 915 (M + Na); exact mass calcd for $C_{41}H_{59}O_{10}F$ (M - oleandrose - water) 730.4092, found 730.4090.

10,11-Dihydroavermectin B1 (2) and 8,11-Dihydro-Δ^9-avermectin B1 (12). To a solution of 1 g (1.0 mmol) of dry **9a** in 10 mL of distilled dichloromethane was added 1 mL of distilled triethylamine, followed by 1.0 g (3 mmol) of dichlorotriphenylphosphorane in one portion. The mixture was stirred at 20 °C for 3 h before TLC analysis (1:1 ethyl acetate/hexane, R_f (sm) = 0.5, R_f(product) = 0.6) indicated completion of reaction. The reaction mixture was flash filtered through a short column of silica gel with 1:1 ethyl acetate/hexane to remove the phosphine oxide and ammonium salt. The filtrate was evaporated in vacuo to afford 950 mg of a yellow glassy solid (identified by NMR as a mixture of allylic chlorides **11a** and **11b**), which was dissolved in 2 mL of toluene and 2 mL of tri-*n*-butyltin hydride. This mixture was then heated in a 100 °C oil bath for 18 h. The cooled mixture was then flash chromatographed on silica gel (3:1 hexane/ethyl acetate) to remove the tin compounds. The isolated product mixture (ca. 2:1 **12a**:**12b** isomer ratio by NMR, a single spot by TLC on silica gel) was further separated by reverse phase HPLC (M20 column, 90:10 methanol/water) to afford 450 mg of 5-*O*-(*tert*-butyldimethylsilyl)-10,11-dihydroavermectin B1 (12a) (eluting first) and 280 mg of 5-*O*-(*tert*-butyldimethylsilyl)-8,11-dihydro-Δ^9-avermectin B1 (**12b**) (next major peak). The former product **12a** was desilylated with HF–pyridine (as described for 10-fluoro-10,11-dihydroavermectin B1, **10b**) to provide **2**, which was indistinguishable from that obtained by hydrogenation of **1**. The latter compound **12b** (280 mg) was desilylated with HF–pyridine to yield 180 mg of **12** as a glassy solid: ^{1}H NMR 0.88 (d, J = 7 Hz, 3 H), 0.93 (d, J = 7 Hz, 3 H), 0.93 (t, J = 9 Hz, 3 H), 1.01 (d, J = 12 Hz, 1 H), 1.05 (d, J = 6 Hz, 3 H), 1.25 (d, J = 6 Hz, 3 H), 1.27 (d, J = 7 Hz, 3 H), 1.40–1.80 (m), 1.58 (s, 3 H), 1.82 (s, 3 H), 2.01 (dd, J = 6, 12 Hz, 1 H), 2.04 (d, J = 10 Hz, 1 H), 2.10–2.44 (m, 6 H), 2.47 (d, J = 2 Hz, 1 H), 3.04 (q, J = 10 Hz, 1 H), 3.16 (dt, J = 2, 9 Hz, 1 H), 3.18 (s, 1 H), 3.22 (t, J = 9 Hz, 1 H), 3.38 (s, 3 H), 3.42 (s, 3 H), 3.43–3.62 (m, 3 H), 3.67 (t, J = 10 Hz, 1 H), 3.75 (m, 2 H), 3.92 (s, 1 H), 3.98 (m, 1 H), 4.02 (d, J = 6 Hz, 1 H), 4.14 (t, J = 9 Hz, 1 H), 4.24 (m, 1 H), 4.73 (d, J = 4 Hz, 1 H), 4.97 (dd, J = 10, 15 Hz, 1 H), 5.11 (dd, J = 3, 10 Hz, 1 H), 5.25 (d, J = 2 Hz, 1 H), 5.32 (m, J = 6 Hz, 1 H), 5.37 (d, J = 4 Hz, 1 H), 5.51 (s, 1 H), 5.60 (dd, J = 3, 10 Hz, 1 H), 5.79 (dd, J = 2, 10 Hz, 1 H), 5.80 (m, 1 H); exact mass calcd for $C_{48}H_{74}O_{14}$ 874.5079, found 874.5091.

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Ionic Chlorination (Bromination) of Alkanes and Cycloalkanes with Methylene Chloride (Bromide)/Antimony Pentafluoride[1]

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Introduction

Halonium ions[2] of cyclic and acyclic nature are of increasing interest as reactive intermediates and reagents

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