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The C4-Exo Methylene Isomer of Avermectin B1a: Synthesis via an Allylic Radical and Bioactivity

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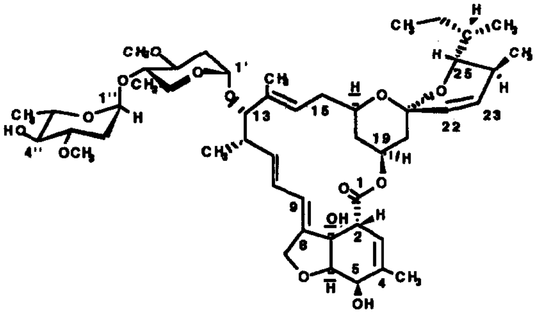
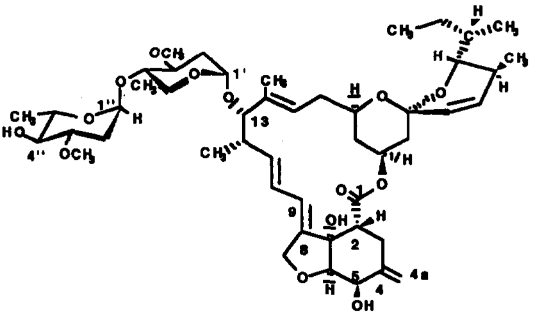
Abstract: Avermectin B_{1a} $\Delta^{4,4a}$, **2**, has been obtained from avermectin B_{1a}, **1**, and its bioactivity evaluated. The key step of the transformation is the reduction of an intermediate allylic radical with nBu_3SnH.

The avermectins are disaccharide derivatives of a structurally similar group of pentacyclic 16-membered lactones with unprecedented insecticidal and antiparasitic activities.[1] Avermectin B_{1a} **1** is the most important member, owing to its high potency against a broad spectrum of endo- and ectoparasites of farm animals and a variety of agricultural pests.[2] Chemical modifications in all of the different regions of these molecules[3] have been undertaken in the hope of improving their biological profile.

The hexahydrobenzofuran unit, **I**, is of primary interest because it is one of the most delicate regions of the molecule. Owing to the presence of the $\Delta^{3,4}$ double bond, C-2 epimerization to give **II** occurs readily, and under basic conditions the $\Delta^{3,4}$ double bond migrates into conjugation to give **III**.[4] Interestingly **II** and **III** do not retain the biological activity of **I**, and hence our laboratory has devoted special attention to the development of strategies to avoid conjugation and epimerization of avermectin derivatives.[5,6] The lack of activities of **II** and **III** indicates the importance of the C-2 configuration, and it seemed to us that relocation of the C-3 double bond in **1** into an exocyclic position, as in **2**, would (a) eliminate the deconjugation problem and (b) reduce the tendency for C-2 epimerization, and provided that no major conformational change would be involved,[7] improved biological properties might result. In this communication we report on this transformation, **1** into **2**, as well as on the bioactivity of **2**.



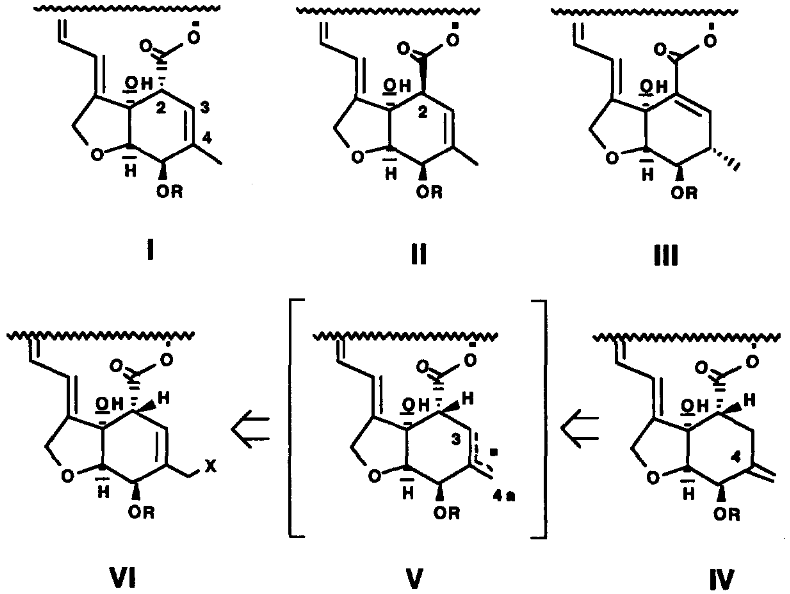
1



2

Reagents involved in the transformation of **1** into **2** should be compatible with the rich functionality of avermectin B$_{1a}$. Since Merck scientists[3g,3o,3r] have shown that tributyltin hydride (Bu$_3$SnH) does not affect the avermectin framework, we decided to explore the feasibility of reduction of an allylic radical,[8,9] **V**, generated at C-4a by homolysis of precursor **VI**. Reduction of **V** at the more reactive secondary site, C-3, would give the desired isomer,[10] **IV**.

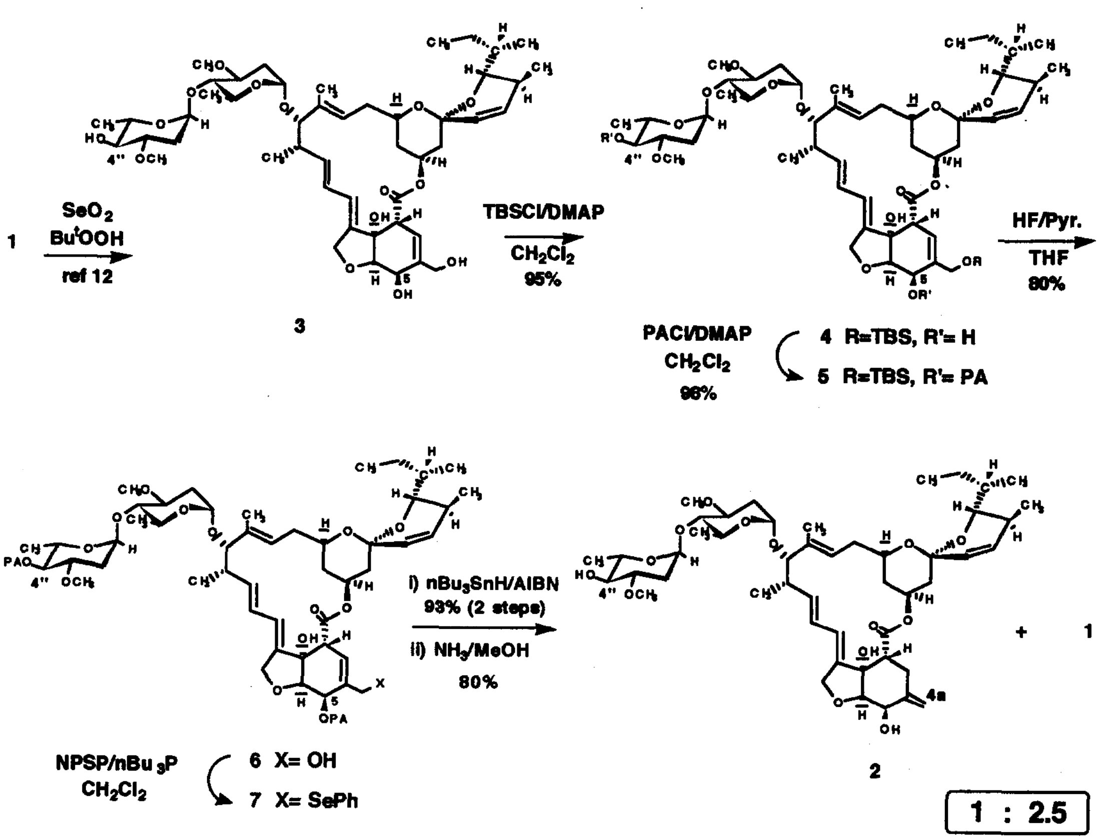
Scheme 1



The C-4a homolisable group of **VI** was envisaged as a phenyl selenide[6b,11] and for its preparation avermectin B$_{1a}$, **1**, was converted into the primary alcohol **3** by selenium dioxide oxidation.[12] Selective protection of the primary hydroxyl group to give **4**, was followed by phenoxyacetylation (PA) of the secondary hydroxyl groups at C-5 and C-4" to give **5**. The C-4a hydroxyl was freed in compound **6**, for phenyl selenation with N-phenylselenophthalimide (NPSP)[13] affording **7** (=**VI** Scheme 1). Treatment of **7** with Bu_3SnH in benzene at 80°C afforded, the desired compound **2**, after deprotection of the phenoxyacetates, together with *avermectin* B_{1a} **1** *(1:2.5* ratio). The stereochemical outcome of the reduction seems to be related to the higher steric accesibility of the primary site of the allylic radical corresponding to **V**.

Biological activity of the synthetic avermectin 2 was found to be as good as in avermectin B_{1a} or ivermectin against some of the adult gastrointestinal helminths of experimentally infected sheep (i.e. *Harmonchus contortus*) **but significantly less potent against others** (i.e. *Ostertagia Circumcita*), **in 0.1 mg/kg dose.**[14] The LD_{50} result indicates that the toxicity is similar to ivermectin.

Scheme 2



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Experimental Section.

Melting points were determined in capillary tubes and are uncorrected. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ). Optical rotations were determined at the sodium D line in chloroform as solvent. ^1H NMR Spectra were recorded at 300 MHz using $CDCl_3$ with $CHCl_3$ as the standard. The coupling constants were verified by homonuclear decoupling experiments. The progress of all reactions was monitored by TLC, which was performed on aluminum plates precoated with silica gel HF-254 (0.2 mm layers) containing a fluorescent indicator. Detection was by UV (254 nm), followed by charring with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g), and cerium sulfate hydrate (5.0 g) in 10% aqueous H_2SO_4 (500 mL). Flash chromatography was performed using Kieselgel 60 (230-400 mesh, Merck) silica gel.

4a-hydroxy-avermectin B1a. (3). To a mixture of SeO_2 (0.13g, 1.1 mmol) and t-butylhydroperoxide (90%, 1mL) in 80 mL of CH_2Cl_2 at room temperature were added 2 g (2.3 mmol) of avermectin B1a **1**. After 14 h the reaction mixture was filtered over Celite evaporated and chromatographed (10% MeOH-CH_2Cl_2) to give 1.32g (65%) of **3**: $[\alpha]_D^{21}$ = +55.1° (c=3.23); m. p. = 164-165°C; ^1H NMR δ 1.29 (3H, d, $J_{12,CH3}$=7.5 Hz, C_{12}-CH_3), 1.50 (3H, s, C_{14}-CH_3), 1.82 (1H, m, 18e-H), 2.03 (1H, m, 20e-H) 2.54 (1H, m, 12-H), 3.18 (1H, t, $J_{4'',5''}$=9 Hz, $J_{3'',4''}$=9 Hz, 4"-H), 3.24 (1H, t, $J_{4',5'}$=9 Hz, $J_{3',4'}$=9 Hz, 4'-H), 3.37 (1H, d, $J_{2,3}$=2.5 Hz, 2-H), 3.42 (3H, s, OCH_3), 3.44 (3H, s, OCH_3), 3.94 (1H, bs, 13-H), 4.01 (1H, d, $J_{5,6}$=5 Hz, 6-H), 4.29 (2H, m, 4a-H, 4b-H), 4.57 (1H, t, $J_{5,6}$=5 Hz, $J_{5,OH}$=5 Hz, 5-H), 4.71 (2H, bs, 8a-H, 8b-H), 4.78 (1H, bs, $J_{1',2a'}$=2.5 Hz, 1'-H), 5.00 (1H, m, 15-H), 5.40 (3H, m, 1"-H, 3-H, 19-H), 5.50 (1H, dd, $J_{22,23}$=10 Hz, $J_{23,24}$=2.5 Hz, 23-H), 5.71-5.91 (4H, m, 9-H, 10-H, 11-H, 22-H). *Anal.* Calcd. for $C_{48}H_{72}O_{15}$: C, 64.83; H, 8.17. Found: C, 64.99; H, 8.34.

4a-*O*-(*tert*-Butyldimethylsilyl)-avermectin B1a. (4). To a stirred solution of the triol **3** (100 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (10 mL) was added NEt_3 (1.7 eq., 0.015 mL), 4-dimethylaminopyridine (DMAP) (10 mg, 0.08 mmol), and *tert*-butyldimethylsilylchloride (TBSCl) (1.5 eq., 25.4 mg). The mixture was stirred at room temperature for 8 h, and then was diluted with CH_2Cl_2, and washed with a saturated solution of $NaHCO_3$. The combined organic extracts were washed with H_2O, dried (Na_2SO_4), and after evaporation of solvent with a rotary evaporator, the crude product was purified by flash chromatography on silica gel using 5% MeOH in CH_2Cl_2 as eluant to give **4** (95.2 mg, 95%): $[\alpha]_D^{21}$ = +34.4° (c=1.29); m. p. = 132-134°C; ^1H NMR δ 0.09 (6H, s, 2x$SiCH_3$), 1.17 (3H, d, $J_{12,CH3}$=7.5 Hz, C_{12}-CH_3), 2.51 (1H, m, 12-H), 3.17 (1H, t, $J_{4'',5''}$=9 Hz, $J_{3'',4''}$=9 Hz, 4"-H), 3.25 (1H, t, $J_{4',5'}$=9 Hz, $J_{3',4'}$=9 Hz, 4'-H), 3.43 (3H, s, OCH_3), 3.45 (3H, s, OCH_3), 3.95 (1H, bs, 13-H), 3.99 (1H, d, $J_{5,6}$=6 Hz, 6-H), 4.25 (1H, AB, $J_{8a,8b}$=14 Hz, 8a-H), 4.38 (1H, AB, $J_{8a,8b}$=14 Hz, 8b-H), 4.49 (1H, t, $J_{5,6}$=6 Hz, $J_{5,OH}$=6 Hz, 5-H), 4.68 (2H, bs, 4a-H, 4b-H), 4.76 (1H, bd, $J_{1',2a'}$=2.5 Hz, 1'-H), 4.97 (1H, m, 15-H), 5.40 (2H, m, 1"-H, 19-H), 5.56 (1H, dd, $J_{22,23}$=10 Hz, $J_{23,24}$=2 Hz, 23-H), 5.65-5.93 (4H, m, 3-H, 10-H, 11-H, 22-H). This compound was characterized as its 4",5-di-*O*-acetate-derivative. $[\alpha]_D^{21}$ = +58.4° (c=2.11). *Anal.* Calcd. for $C_{58}H_{90}O_{17}Si$: C, 64.05; H, 8.32. Found: C, 64.28; H, 8.16.

4a-*O*-(*tert*-Butyldimethylsilyl)-5,4"-di-*O*-phenoxyacetyl-avermectin B1a. (5). To a solution of **4** (100 mg, 0.099 mmol) in dry pyridine (5 mL) at 0°C was added a catalytic amount of DMAP and phenoxyacetyl chloride (PACl) (3 eq., 51 mg, 0.29 mmol). After 3 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O, dried (Na_2SO_4), filtered, evaporated, and the residue chromatographed (3:1 hexane:EtOAc) to afford **5** (123 mg, 98%): $[\alpha]_D^{21}$ = + 42.6° (c=1.91), m.p. = 108-110°C; ^1H NMR δ $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 1.18 (3H, d, $J_{12,CH3}$=7.5 Hz, C_{12}-CH_3), 1.50 (3H, s, C_{14}-CH_3), 1.80 (1H, m, 20eq.-H), 2.05 (1H, m, 18eq.-H), 2.52 (1H, m, 12-H), 3.22 (1H, t, $J_{4',5}$=9 Hz, $J_{3',4'}$=9 Hz, 4'-H), 3.32 (3H, s, OCH_3), 3.39 (1H, m, 2-H), 3.42 (3H, s, OCH_3), 3.80-3.97 (3H, m, 5"-H, 5'-H, 13-H), 4.12 (1H, bs, 17-H), 4.17 (1H, d, $J_{5,6}$=6 Hz, 6-H), 4.99 (1H, m, 15-H), 5.41 (2H, m, 1"-H, 19-H), 5.51 (1H, dd, $J_{22,23}$=10 Hz, $J_{23,24}$=2.5 Hz, 23-H), 5.70-5.90 (5H, m, 3-H, 5-H, 10-H, 11-H, 22-H), 6.90-7.32 (10H, m, arom.). *Anal.* Calcd. for $C_{70}H_{98}O_{19}Si$: C, 66.11; H, 7.77. Found: C, 66.40; H, 7.92.

4a-hydroxy-5,4"-di-*O*-phenoxyacetyl-avermectin B1a. (6). A stock solution of hydrogen fluoride in pyridine was prepared from 1 mL of the commercial reagent (Aldrich) in dry THF (7 mL) and addition of dry pyridine (2 mL) to make 10 mL of the stock solution. A portion of the solution (5 mL) and 300 mg (0.23 mmol) of **5** was stirred for 2 h at room temperature. After dilution with Et_2O, washing with cold saturated $NaHCO_3$ solution, drying (Na_2SO_4), filtration, and evaporation, a semi-solid was obtained which was chromatographed (3:2 hexane:EtOAc) to give solid **6** (218 mg, 80%): $[\alpha]_D^{21}$ = +38.9°, (c=1.5), m.p.=120-122°C; ^1H NMR δ 1.18 (3H, d, $J_{12,CH3}$=7.5 Hz, C_{12}-CH_3), 1.51 (3H, s, C_{14}-CH_3), 2.05 (1H, m, 18eq.-H), 2.55 (1H, m, 12-H), 3.24 (1H, t, $J_{4',5'}$=9 Hz, $J_{3',4'}$=9 Hz, 4'-H), 3.32 (3H, s, OCH_3), 3.45 (3H, s, OCH_3), 3.49 (1H, bd, $J_{24,25}$=10 Hz, 25-H), 3.97 (1H, bs, 13-H), 4.09 (1H, bs, 17-H), 4.18 (1H, d, $J_{5,6}$=6 Hz, 6-H), 5.01 (1H, m, 15-H), 5.41 (2H, m, 1"-H, 19-H), 5.57 (1H, dd, $J_{22,23}$=10 Hz, $J_{23,24}$=2.5 Hz, 23-H), 5.70-5.92 (5H, m, 5-H, 9-H, 10-H, 11-H), 5.95 (1H, bs, 3-H), 6.90-7.31 (10H, m, arom.). *Anal.* Calcd. for $C_{64}H_{84}O_{19}$: C, 66.40; H, 7.32. Found: C, 66.22; H, 7.16.

5,4"-di-*O*-phenoxyacetyl-$\Delta^{4,4a}$-avermectin B1a. (8). To a stirred solution of **6** (100 mg, 0.086 mmol) in dry CH_2Cl_2 (10 mL) at 0°C were added n-tributylphosphine (35 mg, 0.17 mmol) and N-(phenylseleno)phthalimide (NPSP) (39.2 mg, 0.13 mmol). The mixture was stirred at room temperature for 2 h. After evaporation of the solvents, the oily product was chromatographed (7:3 hexane:EtOAc) and the product obtained was used directly for the next step. The phenyl selenide **7** was dissolved in dry degassed toluene (20 mL) and the solution was brought to reflux. To the boiling solution, was added *via* syringe pump over a period of 7 h, a catalytic amount of AIBN and n-tributyltinhydride (26.6 mg, 0.09 mmol), dissolved in 5 mL of dry toluene. The solvent was then evaporated and the mixture chromatographed (1:1:1, hexane:Et_2O:CH_2Cl_2) to give **8** (26 mg): ^1H NMR δ 1.50 (3H, s, C_{14}-CH_3) 3.22 (1H, t, $J_{4',5'}$=8 Hz, $J_{3',4'}$=8 Hz, 4'-H), 3.32 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 3.45 (1H, bd, $J_{25,24}$=10 Hz, 25-H), 3.92 (1H, bs, 17-H), 3.95 (1H, d, $J_{5,6}$=5 Hz, 6-H), 4.93 (1H, bs, 4a-H), 4.95 (1H, m, 15-H), 5.02 (1H, bs, 4b-H), 5.40 (1H, bd, $J_{1'',2a''}$=2.5 Hz, 1"-H), 5.43 (1H, m, 19-H), 5.55 (1H, dd, $J_{23,22}$=10 Hz, $J_{23,24}$=3 Hz, 23-H), 5.70 (1H, t, $J_{4'',5''}$=8 Hz, $J_{3'',4''}$=8 Hz, 4"-H), 5.73-5.82 (4H, m, 9-H, 10-H, 11-H, 22-H), 6.91-7.30 (10H, m, arom.), characterized as its dephenoxyacetylated analog **2**.

$\Delta^{4,4a}$-avermectin B1a. (2). Gaseous NH_3 was bubbled into a solution of **7** (20 mg, 0.017 mmol) in MeOH (5 mL) at 0°C for 10 min. After complete disappearance of the starting material (TLC) the organic solvent was evaporated and the crude product chromatographed to give **2** (12 mg, 80%): $[\alpha]_D^{21}$ = +195.4° (c=0.4); ^1H NMR δ 1.15 (3H, d, $J_{12,CH3}$=7.5 Hz, C_{12}-CH_3), 1.50 (3H, s, C_{14}-CH_3), 1.73 (1H, m, 20eq.-H), 1.95 (1H, m, 18eq.-H), 2.50 (1H, m, 12-H), 3.16 (1H, t, $J_{4'',5''}$=10 Hz, $J_{3'',4''}$=10 Hz, 4"-H), 3.24 (1H, t, $J_{4',5'}$=10 Hz, $J_{3',4'}$=10 Hz, 4'-H), 3.47 (3H, s, OCH_3), 3.64 (2H, m, 3"-H, 3'-H), 3.75-3.95 (5H, m, 5"-H, 5'-H, 6-H, 13-H, 17-H), 4.43 (1H, m, 5-H), 4.58 (2H, s, 8a-H, 8b-H), 4.76 (1H, bd, $J_{1',2a'}$=3 Hz, 1'-H), 4.95 (1H, m, 15-H), 5.03 (1H, bs, 4a-H), 5.21 (1H, bs, 4b-H), 5.41 (1H, bd, $J_{1'',2a''}$=3 Hz, 1"-H), 5.44 (1H, m, 19-H), 5.54 (1H, dd, $J_{22,23}$=10 Hz, $J_{23,24}$=2.5 Hz, 23-H), 5.64-5.81 (4H, 9-H, 10-H, 11-H, 22-H). *Anal.* Calcd. for $C_{48}H_{72}O_{14}$: C, 66.02; H, 8.32. Found: C, 66.31; H, 8.17.

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