Preparation of Intact Hexahydrobenzofuran Subunits of Ivermectin by Selective Ozonolysis of the $\Delta^{3,4}$-Intermediate Secoester

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Avermectins, and especially their semi-synthetic partial hydrogenation adduct Ivermectin, constitute a potent endectocide family of worldwide veterinary use that has been known for more than twenty years and has also demonstrated a great efficacy in the treatment of various human filariasis diseases. In a program to design new access to cost-effective analogues with a new or optimised medical profile, we decided to develop a practical synthetic strategy starting from southern subunits cut from commercial Ivermectin, which is now easily available at a reasonable price. We describe here the first process for preparing intact hexahydrobenzofuran subunits by controlled degradation of Ivermectin in a basically three-step process that totally preserves the integrity of the Δ^3 unsaturated pattern of the unit, which is a requisite feature for the biological activity of this family of molecules. The two crucial steps of the sequence, developed here on a gram scale, involve a transesterification reaction in the presence of titanium(IV) alkoxide that allows the macrolactone opening without isomerisation in 55–70 % yields, followed by the selective ozonolysis of the C10–C11 double bond in the presence of different reducting agents to afford the expected southern unit in reasonable yields.

Introduction

For more than 20 years the the avermectins and milbemycins have revolutionized antiparasitic and antipest control in animal health care,[1] and have also been used in public health programs against global diseases.[2] These molecules, as well as a number of semi-synthetic materials, exhibit unprecedentedly potent insecticidal and antihelmintic activities that make them the most important pesticides and veterinary drugs ever developed. Moreover, their unique pharmacological activity against various endemic human filariasis diseases in tropical countries endow them with a strategic medicinal role, which is particularly illustrated in the global treatment of onchocerciasis (river blindness) or, more recently, lymphatic filariasis.[3] This unique biological profile, as well as the complex challenging chemical structure of the avermectin macrolides,[4] has triggered huge synthetic efforts that have resulted in several total syntheses of avermectin members, either in the B1a[5] or in the A1a series.[6] Syntheses of the most complex members of the milbemycin family, which lack the hydroxyl group at C-13 but possess the same hexahydrobenzofuran (HHBF) C1–C10 subunit as avermectins, have also been reported.[7] For our own part, several years ago we described a total synthesis of the aglycon of 22,23-dihydroavermectin B1b, the major component of the semi-synthetic marketed antiparasitic agent Ivermectin (IVM), a selective 22,23-double bond hydrogenation product prepared from a mixture of natural avermectins.[8]

Besides the academic challenge, studies towards the total synthesis of avermectins are of strategic importance in establishing the unique chemical behaviour of these molecules as well as delineating the main chemical guidelines for the future preparation of derivatives or analogues. Moreover, the first-line economic and biological importance of this class of compounds is continuously stimulating efforts to develop new structurally modified avermectins with enhanced activity or different selectivity profiles, together with lower toxicity. Two particular points of interest are currently the focus of attention in the fight against helminths and stimulate the search for new drugs: the increased resistance to the classical avermectin/milbemycin molecules, especially in the case of veterinary applications,[9] and the inability of these molecules to act against macrofilarae, a point of particular interest in human medicine.[10]

Starting from fermentation pools, convenient modification procedures have led to innumerable avermectin analogues, many of which have been patented, and some of

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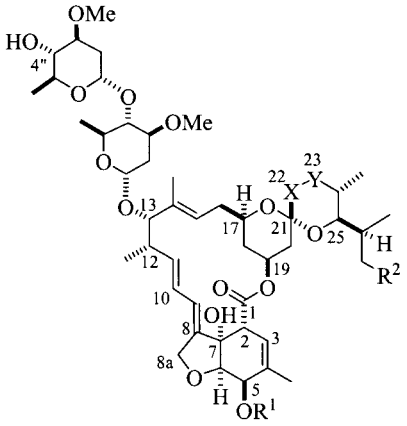


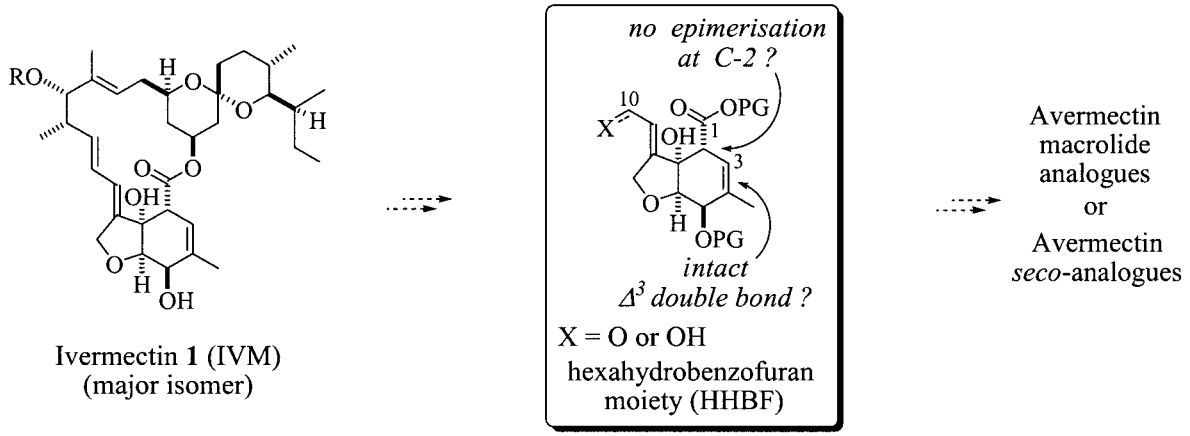
		R^1	X–Y	R^2
Avermectins	A1a	Me	CH=CH	Me
	A1b	Me	CH=CH	H
	A2a	Me	CH_2–CH(OH)	Me
	A2b	Me	CH_2–CH(OH)	H
	B1a	H	CH=CH	Me
	B1b	H	CH=CH	H
	B2a	H	CH_2–CH(OH)	Me
	B2b	H	CH_2–CH(OH)	H
Ivermectin **1** (maj.)		H	CH_2–CH_2	Me

these have already found specific applications, particularly for veterinary purposes.[11] Although the continuous chemistry efforts so far developed have resulted in convenient processes to modify almost each part of these molecules, no practical strategy has yet been described to prepare avermectin analogues with a modified macrocycle skeleton. Owing to the complexity and tediousness of the processes still required to achieve total syntheses of such molecules, alternative methods have to be found to develop a practical and cost-effective preparation of novel analogues with a modified macrocycle core.

Within a project devoted to elaborating molecular candidates potentially superior to natural avermectins or their already known analogues for use in human medicine, particularly in developing countries, we decided to develop a synthetic strategy that allows the preparation of skeleton-modified avermectin analogues in pharmacologically required gram-scale quantities.

Due to its well-established pharmacological importance in the observed biological activities of avermectins, the HHBF moiety was defined as the central core from which all analogues have to be planned. However, its high structural complexity and liability still represent a major obstacle to the development of a practical total synthesis of this subunit for which, apart from the aforementioned total syntheses, several alternative synthetic approaches have specifically been proposed.[12] We therefore decided to address a semi-synthesis of macrolide-modified avermectin analogues, starting from intact HHBF subunits obtained by controlled fragmentation of commercial Ivermectin (**1**) according to Scheme 1.[13] This paper deals with our results on the preparation of such intact HHBF subunits according to this strategy. It is important to emphasise that the HHBF subunit derivatives themselves can be also regarded as seco-analogues of avermectins and therefore represent potential pharmaceutical targets.

Although various attempts to obtain HHBF subunits from avermectins have already been described in the literature, the approaches developed so far sacrifice the crucial $\Delta^{3,4}$ non-conjugated ester function, which is a requisite structural feature to preserve the activity of these molecules.[14] Hanessian's precedent, developed during the preparation of HHBF subunits from natural avermectins to complete the synthesis of avermectin B1a, involves an alkaline opening of the macrolide nucleus of natural avermectin B1a to a conjugated $\Delta^{2,3}$ secoester prior to a controlled ozonolysis in the presence of Sudan Red B, which delivers a conjugated $\Delta^{2,3}$ HHBF.[15] The latter subunit was sub-



Scheme 1.

sequently condensed to a synthetic northern subunit.[16] Such an approach requires a critical deconjugation of the $\Delta^{2,3}$ double bond during the last steps of the macrolide synthesis.[17] Despite this drawback, this strategy has already been applied to the synthesis of some avermectin analogues.[18] Another example of the tentative recovery of HHBF subunits involves oxidative scission of the C8–C9 double bond along with reduction of the ester function.[19]

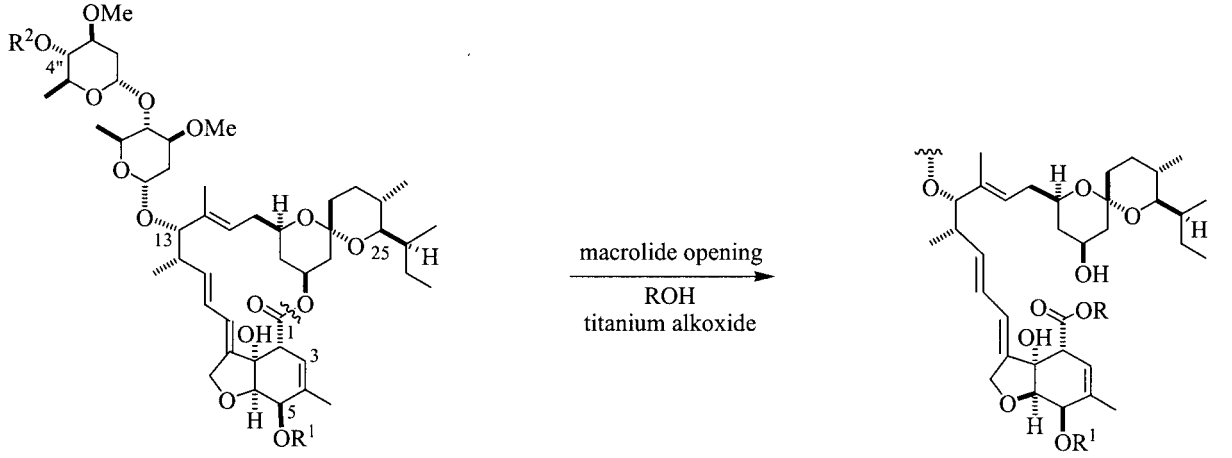
Based on our precedents for the opening of the avermectin macrolide nucleus without conjugation of the $\Delta^{3,4}$ double bond,[20] we chose a strategy involving a two-step process where a mild preliminary transesterification reaction of **1** to give the corresponding secoester is followed by a selective ozonolysis of the C10–C11 double bond of the intermediate secoester to deliver the expected southern subunit. However, because of a report from Merck's group describing the ozonolysis of avermectin A2a where apparently no HHBF-type compounds were isolated,[21] a great uncertainty remained concerning the conditions favourable for such a selective ozonolysis of avermectin secoesters having a non-conjugated $\Delta^{3,4}$ double bond.

Results and Discussion

A preliminary requisite before developing the planned sequence was the need for a protection of the 5-OH and 4′′-OH hydroxyl groups. Treatment of commercial Ivermectin with (*tert*-butyldimethylsilyl) chloride under known conditions, followed by column chromatography, furnished the expected 5-*O*-(*tert*-butyldimethylsilyl) Ivermectin **2** (5-*O*-TBDMS-IVM, 79% yield), along with the less polar 4′′,5-bis-*O*-(*tert*-butyldimethylsilyl) Ivermectin **3** (4′′,5-bis-*O*-TBDMS-IVM, 22% yield, slightly contaminated with silanol by-products).[22] In order to check the overall influence of the protection of these hydroxyl groups on the course of the subsequent reaction sequence, both the mono- and the bis-silylated derivatives as well as the non-protected IVM **1** itself were investigated.

Transesterification Reactions

These reactions were carried out from the preceding differently protected Ivermectin derivatives **1**–**3** using See-



1: $R^1 = R^2 = H$ (IVM)
2: $R^1 = H$; $R^2 = TBS$ (5-*O*-TBS-IVM)
3: $R^1 = R^2 = TBS$ (4",5-bis-*O*-TBS-IVM)

4: (IVM secoester)
5: (5-*O*-TBS-IVM secoester)
6: (4",5-Bis-*O*-TBS-IVM secoester)

Scheme 2.

Table 1. Transesterification reactions in the presence of various primary alcohols.

Entry	Starting material (SM)	mmols (g)	Alcohol	Lewis acid 1 equiv.	Work-up[a]	Temp. (oil bath)	Recovered SM yield[b]	Secoester yield[b]	
1	IVM (**1**)	7.0 (6.16)	ethanol	Ti(*i*OPr)$_4$	SP	110 °C	31%	**Et-4**	37%[d]
2	IVM (**1**)	2.0 (1.75)	ethanol	Ti(OEt)$_4$[c]	LP	110 °C	10%	**Et-4**	68%
3	5-*O*-TBS-IVM (**2**)	2.0 (1.97)	β-trimethylsilyl ethanol	Ti(*i*OPr)$_4$	SP	110 °C	6%	**TSE-5**	45%[d]
4	5-*O*-TBS-IVM (**2**)	5.0 (4.93)	isoamyl alcohol	Ti(*i*OPr)$_4$	SP	110 °C	1%	***i*Amyl-5**	60%[d]
5	5-*O*-TBS-IVM (**2**)	1.9 (1.92)	methanol	Ti(*i*OPr)$_4$	SP	110 °C	8%	**Me-5**	54%[e]
6	5-*O*-TBS-IVM (**2**)	4.0 (3.94)	ethanol	Ti(*i*OPr)$_4$	SP	110 °C	2%	**Et-5**	56%[d]
7	5-*O*-TBS-IVM (**2**)	4.0 (3.94)	ethanol	Ti(OEt)$_4$	SP	110 °C	18%	**Et-5**	38%
8	5-*O*-TBS-IVM (**2**)	8.0 (7.89)	ethanol	Ti(OEt)$_4$	LP	110 °C	5%	**Et-5**	61%
9	5-*O*-TBS-IVM (**2**)	8.2 (8.14)	ethanol	Ti(OEt)$_4$	LP	90 °C	–	**Et-5**	59%
10	4′′,5-bis-*O*-TBS-IVM (**3**)	6.0 (6.59)	ethanol	Ti(OEt)$_4$	LP	90 °C	–	**Et-6**	57%

[a] SP: solid-phase work-up; LP: liquid-phase work-up. [b] All yields refer to purified products. [c] 1.5 equiv. of Ti(OEt)$_4$. [d] Products contaminated with minor amounts of the corresponding isopropyl secoester. [e] Isolated together with 14% of the less-polar isopropyl secoester *i*Pr-**5**.

bach's titanium(IV) isopropoxide conditions, which have already successfully been applied by us, to furnish the secoesters **4**–**6** (Scheme 2).[23]

The course of the transesterification reactions was monitored by TLC until total consumption of the starting material or apparent equilibrium of the reaction mixture composition. In some cases, the reaction was quenched earlier due to the occurrence of degradation by-products. All secoesters were purified by flash chromatography and thoroughly identified, mainly by ^{13}C NMR spectroscopy. The signals of the carboxyl carbon at δ = 173.5–174.0 ppm, together with the presence of a ^{1}H NMR signal at δ = 1.80 ppm for the Me at C-4, were of diagnostic value to determine the preservation of the non-conjugated double bond at C3–C4. In the case of conjugation of the double bond at C2–C3, the carboxyl ^{13}C signals shifted upfield to δ = 168–169.5 ppm. The main results obtained in the presence of various primary alcohols are summarised in Table 1.

All preliminary experiments (entries 1 and 3–6) were carried out using our already reported standard conditions (reflux or 110 °C, titanium(IV) isopropoxide then solid-phase work-up) and ethanol was chosen as the standard alcohol. For the transesterification of mono-protected **2**, regarded as the most significant intermediate for further synthetic applications, several other primary alcohols were used, including β-trimethylsilyl ethanol and its corresponding isosteric congener isoamyl alcohol.[24] Under these standard conditions, protection of the 5-OH group was found to be necessary to get acceptable yields (entry 1 vs. entry 6). In all cases, strictly anhydrous conditions were required to get reproducibly good yields, which is markedly different from Seebach's original conditions.

Some noticeable observations and improvements are worthy of comment. Careful examination of the ^{13}C NMR spectra of various samples of ethyl secoester **Et-5** obtained by scale-up of the transesterification reaction with ethanol in the presence of titanium(IV) isopropoxide (entries 1 and 3–6) revealed contamination with minor amounts of the corresponding inseparable isopropyl secoester (***i*Pr-5**), which results from an unexpected competing reaction with the bulkier isopropyl ligand of the titanium atom (peaks of *i*Pr-methyl groups at δ = 21.6 and 21.7 ppm).[25] Owing to more favourable polarity differences, the minor isopropyl secoester ***i*Pr-5** was successfully isolated and characterised at the outset of the transesterification reaction with methanol (entry 5). In the case of the ethyl secoesters, the formation of this undesirable by-product was subsequently avoided by using titanium(IV) ethoxide, prepared from commercial [Ti(O*i*Pr)$_4$] by a preliminary ethanol/2-propanol exchange, followed by distillation. Substitution of the solid-phase (SP) work-up by a classical liquid-phase (LP) extraction resulted in improved yields of the secoesters, particularly in the case of the most polar non-silyl-protected secoester **Et-4** (entry 2; see also entries 8 and 9). In the case of reactions in the presence of the more active titanium(IV) ethoxide, lowering of the reaction temperature from 110 °C to 90 °C (oil bath) led to a decrease in the formation of the TLC-observable by-products.

Under these improved conditions, the pure ethyl secoesters **Et-4**, **Et-5** and **Et-6** can be repproducedly obtained in 57–68% yields on a 2–8-g scale (entries 2 and 8–10).

Selective Ozonolysis of the C10–C11 Double Bond

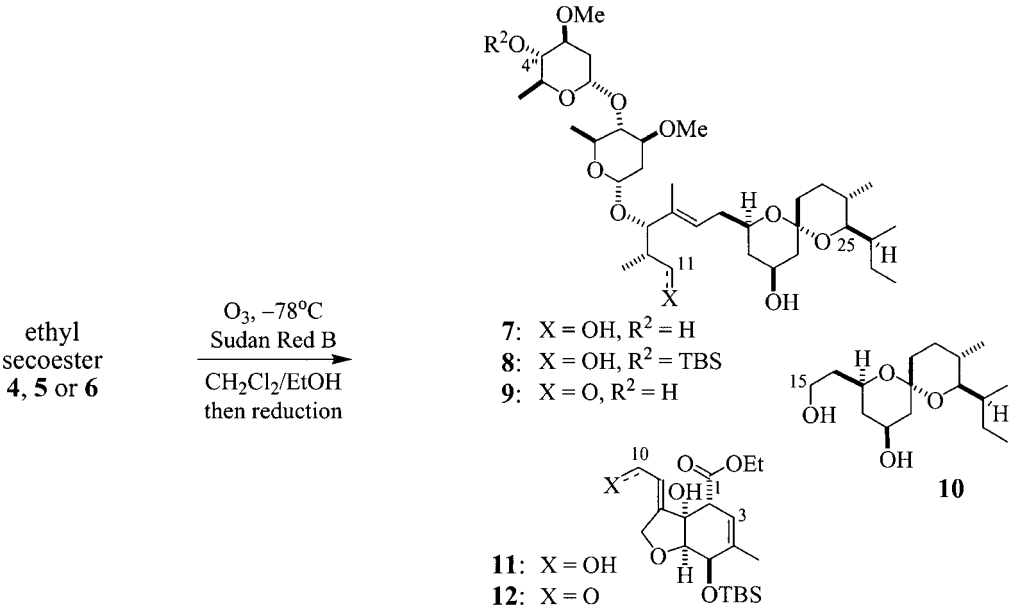
The preceding ethyl secoesters were subsequently submitted at –78 °C to a selective ozonolysis reaction in a dichloromethane/ethanol mixture in the presence of Sudan Red B. During preliminary work, the course of the ozonation reaction was carefully monitored by TLC until apparent total consumption of the starting secoester. After elimination of the excess of ozone with nitrogen, sodium borohydride (added in methanol at 0 °C) or dimethyl sulfide (neat) were added to the reaction mixture as reducing agents to furnish the expected primary alcohol or aldehyde, respectively. Acidic work-up followed by silica gel column chromatography of the extract afforded the southern HHBF subunit as well as the corresponding northern moiety (Scheme 3). The main results are summarised in Table 2.

No HHBF subunit was recovered when the non-protected ethyl secoester **Et-4** was tentatively ozonized (entry 1). A possible explanation for this is the oxidation of the $\Delta^{3,4}$ double bond due to the well-known propensity of an allylic alcohol function to produce anomalous ozonolysis adducts.[26] This result emphasises the importance of the protecting group at C-5 and further studies have to be performed to optimise its choice.

The ozonolysis of the mono-silyl-protected ethyl secoester **Et-5** (entries 2–5), as well as of the di-protected **Et-6** (entry 6), with the $NaBH_4$ reducing protocol, gave the expected HHBF alcohol **11** together with the northern alcohol **7** or **8**, respectively. All reactions furnished better yields of the northern subunit (56–80% yield) than the HHBF counterpart (33–53%). Care has to be taken to avoid over-oxidation of the secosesters: in some cases spirodiol **10**, which results from oxidative scission of the C14–C15 double bond, was isolated (see entry 3). This diol is difficult to separate from HHBF alcohol **11**. In one experiment (entry 5), crude **Et-5** was directly submitted to the ozonolysis reaction to provide alcohol **11** in an overall yield of 31% from **2**, which compares well with the 30% average two-step yield obtained when purifying the intermediate secoester.

Addition of dimethyl sulfide to the dichloromethane/ethanol ozonide solution prepared from **Et-5** according to the above conditions furnished the expected aldehyde **12** in 57% yield after column purification, together with the northern aldehyde **9** (77%).

Experiments were carried out in order to shed light on the reason(s) for the lower yields obtained in the case of the HHBF subunits when compared to the northern counterpart. Direct treatment of secoester **Et-5** with a large excess of sodium borohydride at room temperature (15–16 h in dichloromethane/ethanol/methanol, TLC monitoring) led to the clean reduction of the ester function to give the corresponding Ivermectin secoalcohol (total disappearance of the ^{13}C NMR signal at δ = 173.72 ppm in the crude extract,



Scheme 3.

Table 2. Reductive ozonolysis reactions of intermediate ethyl secoesters.

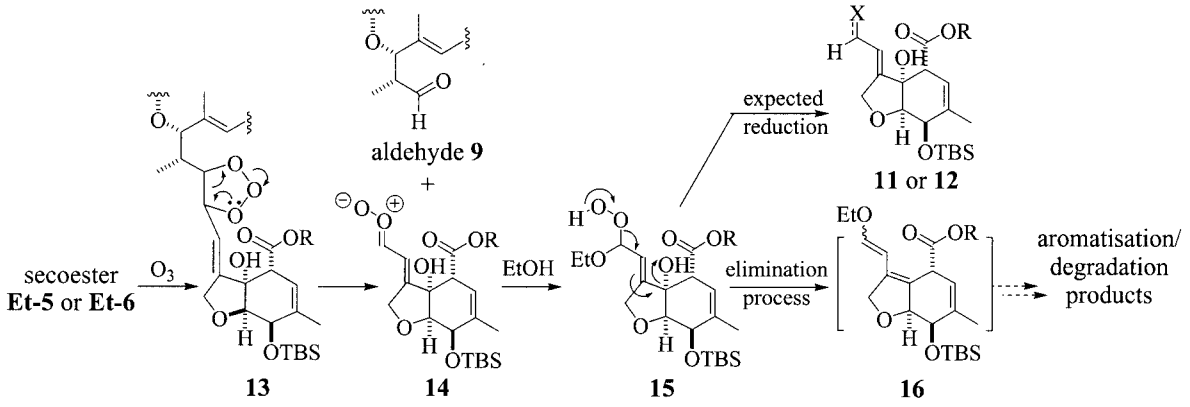
Entry	Starting material	mmols (g)	Reducing agent (equiv.)	Reduction time (temp.)	Northern subunit yield[a]		HHBF subunit yield[a]	
1	**Et-4**	0.9 (0.84)	$NaBH_4$ (12)	30 min (–78 °C) then 30 min (0 °C)	**7**	45%	no product	
2	**Et-5**	3.3 (3.43)	$NaBH_4$ (4)	30 min (–78 °C) then 30 min (0 °C)	**7**	63%	**11**	33%
3	**Et-5**	2.3 (2.36)	$NaBH_4$ (12)	30 min (–78 °C) then 30 min (0 °C)	**7**	80%	**11**	49%[b]
4	**Et-5**	1.5 (1.51)	$NaBH_4$ (5)	25 min (0 °C)	**7**	75%	**11**	53%
5	**Et-5**	6.5 (6.73)[c]	$NaBH_4$ (12)	30 min (–78 °C) then 30 min (0 °C)	**7**	43% (2 steps)	**11**	31% (2 steps)
6	**Et-6**	0.87 (1.00)	$NaBH_4$ (5)	16 min (0 °C)	**8**	62%	**11**	37%
7	**Et-5**	1.4 (1.50)	Me_2S (5)	overnight (room temp.)	**9**	77%	**12**	57%

[a] All yields refer to purified products. [b] Product contaminated with about 2% of spirodiol **10**. [c] Crude ethyl secoester **Et-5** was used.

see Experimental Section). Interestingly, under the same conditions the parent macrolide 5-*O*-TBS-IVM (**2**) was found to be significantly more stable than the corresponding secoester; it affords several decomposition products only after prolonged reaction times at room temperature. Although the reduction conditions used during the ozonolysis process were slightly smoother than those required for the ester reduction, this collateral ester reduction could be responsible, at less partially, for the loss of yield of the HHBF alcohol. It can also account for the slightly higher yields observed in the case of dimethyl sulfide reduction.

Careful study of the course of the ozonolysis reaction, including by TLC and recording the ^{13}C NMR spectrum of the crude intermediate ozonide adduct, revealed that the northern aldehyde **9** is already present before addition of any reducing agent (^{13}C NMR signal at δ = 204.21 ppm).[27] The corresponding HHBF aldehyde **12**, which is also detected in the ^{13}C NMR spectrum (signal at δ = 190.14 ppm), was not initially present in the TLC control and must therefore be formed during the subsequent work-up of the sample, although the origin of the reduction process is not clear. Therefore, the reaction can be supposed to proceed, according to the classical Criegee mechanism,[28] via the primary ozonide **13**, which is subsequently regioselectively cleaved to provide the northern aldehyde **9** and the carbonyl oxide **14**, as shown in Scheme 4. Nucleophilic addition of ethanol to the latter activated intermediate in situ furnishes, instead of the classical secondary ozonide, the ethoxy hydroperoxide **15**, which is subsequently transformed into the reduced southern unit **11** or **12**.

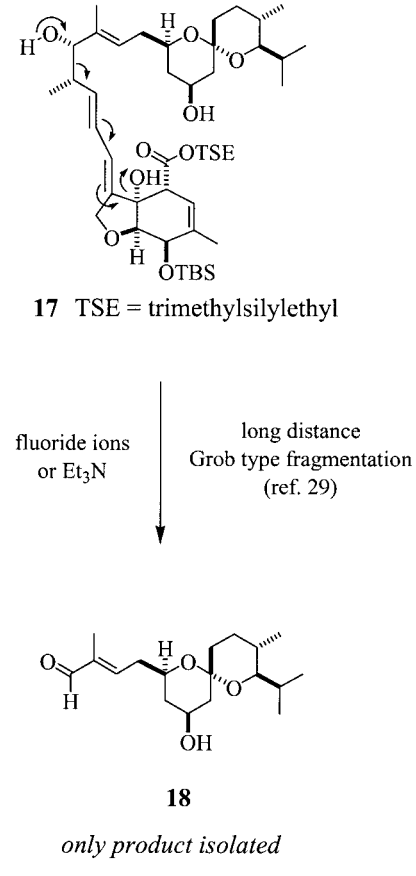
Alternatively, according to a competing degradation process, intermediate **15**, due its high liability, could undergo a conjugated elimination reaction to give an unstable conjugated enol ether such as **16**, which can subsequently continue to degrade. However, all attempts to characterise and isolate further transformation products from the HHBF subunit of Ivermectin, i.e. elimination or aromatisation products, were unsuccessful. Interestingly, such a conjugate elimination process is reminiscent of a degradation reaction previously observed in our laboratories during the synthesis of Ivermectin aglycon. Several attempts to deprotect the ester function of the intermediate secoester **17** under various basic conditions afforded the C13–C25 aldehyde **18** as the only isolable adduct (Scheme 5).[29] We were unable to char-



Scheme 4.

acterise any other by-product occurring from the southern moiety. A long-range, Grob-type fragmentation reaction, a formal vinylog of the degradation reaction postulated for **15**, could account for the observed formation of **18**.

Despite the lack of evidence of a mechanism inducing a collateral degradation of the HHBF subunits, the clean regioselectivity observed for the cleavage of the primary ozonide **13** from the parent secoesters is probably critical in the scission process and will probably offer some further synthetic perspectives for the preparation of useful intermediates from natural avermectins.



Scheme 5.

Conclusions

The three-step process described here allows rapid preparation of the intact hexahydrobenzofuran subunit **11** or its corresponding aldehyde **12** from Ivermectin in acceptable yields on a gram scale. No trace of conjugated $\Delta^{2,3}$ HHBF subunit was detected in any case. Further studies are currently underway to synthesise new avermectin analogues from these molecules as well as to test simple derivatives of these subunits themselves on different biological targets of pharmacological interest.

Experimental Section

General Remarks: Optical rotations were determined on Schmidt–Haensch, Polartronic NH8 or Polartronic E instruments. Mass spectra were obtained on a Micromass ZQ 4000 spectrometer by direct introduction by electron-spray. The high-resolution, high-mass-accuracy measurements were performed either on a Micromass Autospec mass spectrometer with EBE configuration using 70 eV electron ionisation (EI) at the Instituto de Química, Campinas, Brazil or on a Micromass ZABSpecTOF spectrometer at the Centre Régional de Mesures Physiques de l'Ouest, CRMPO, France, using electron spray ionisation and MeOH as solvent (4 kV acceleration, 60 °C source temperature). Infrared spectra were obtained in potassium bromide on a Nicolet-Nexus 670 model instrument (wavelengths are given in wavenumbers). ^{1}H NMR spectra were recorded on a Bruker DRX 400 instrument. The chemical shifts (δ) are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). Coupling constants (J) are given in Hertz (Hz). ^{13}C NMR spectra were recorded on a Bruker AC 200 instrument at 50.32 MHz or on a Bruker DRX 400 instrument at 100.62 MHz. The chemical shifts are expressed in parts per million (ppm), and are referenced to residual chloroform (δ = 77.0 ppm).

DMF was distilled from potassium hydroxide and ethanol, and ethanol, β-(trimethylsilyl) ethanol and isoamyl alcohol from magnesium. Dichloromethane was distilled from calcium hydride. Hexane and ethyl acetate were distilled before flash chromatography. Thin layer chromatography (TLC) was performed with precoated plates of silica gel 60F 254 (Merck, Art 7735). Flash chromatography was performed with silica gel Merck 60, 230–400 mesh (Art, 9385).

The commercial Ivermectin {$[a]_D$ = +34.8 (c = 1.00, $CHCl_3$)} used throughout this work was a mixture of 22,23-dihydroavermectin B1a and B1b, in a ratio greater than 97:3 (HPLC analysis) and is

therefore described throughout this paper as the B1a constituent. This material was kept under high vacuum for several hours before use. Most of the reagents (Aldrich) were used without treatment, except titanium(IV) isopropoxide [Ti(O*i*Pr)$_4$], which was distilled under reduced pressure (170–190 °C, 5–10 torr) and stored under nitrogen. Titanium(IV) ethoxide [Ti(OEt)$_4$] was obtained from [Ti(O*i*Pr)$_4$] by refluxing with anhydrous ethanol, followed by distillation under reduced pressure (150–170 °C, 5–10 torr), and stored under nitrogen. Ozone was obtained from a BMT 802 ozone generator (BMT Messtechnik GMBH, Berlin, Germany) and the enriched ozone stream was controlled using a flow rotameter.

Probably due to the mode of purification (single preparative silica column followed by solvent evaporation) and the known proclivity of avermectin members to fix solvent or water molecules, attempted elemental analyses did not agree with the usual 0.4% accuracy.

The carbon numbering of the intermediates and of the final compounds is given according to standard numbering of avermectins/Ivermectin to simplify the analysis.

Ivermectin Protection: Imidazole (9.35 g, 137.26 mmol, 4.0 equiv.) and DMAP (0.84 g, 6.84 mmol, 0.2 equiv.) were added to a solution of Ivermectin (**1**; 30.00 g, 34.30 mmol) in 180 mL of DMF at room temperature, followed by TBDMSCl (15.51 g, 102.90 mmol, 3.0 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 20 h and monitored by TLC. Diethyl ether (500 mL) and water (500 mL) were then added, the aqueous layer was washed with diethyl ether (4 × 200 mL), and the combined ether extracts were washed with brine (2 × 200 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give, in order of elution, after purification by flash chromatography on silica gel (hexanes/AcOEt mixtures from 100:0 to 0:100), 12.15 g of 4′′,5-bis-*O*-(*tert*-butyldimethylsilyl) Ivermectin (**3**; yellow oil, contaminated with silyl reagent by-product), 26.96 g of 5-*O*-(*tert*-butyldimethylsilyl) Ivermectin **2** (white solid, 79%) and 0.46 g (1.5%) of recovered Ivermectin **1**. Further treatment of the bis-silylated fraction at 70 °C under high vacuum gave 8.26 g (22%) of 4′′,5-bis-*O*-(*tert*-butyldimethylsilyl) Ivermectin (**3**), still slightly contaminated with silanol by-product.

4′′,5-Bis-*O*-(*tert*-butyldimethylsilyl) Ivermectin (3): IR (KBr): $\tilde{\nu}$ = 3475, 3000–2850, 1714, 1472, 1463, 1379, 1255, 1200–1000, 987, 871, 836, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (br. d, J = 8.6 Hz, 1 H, H-9), 5.79–5.65 (m, 2 H, H-10 and H-11), 5.32 (br. s, 3 H, H-1′′, H-3 and H-19), 4.99 (br. d, J = 9.4 Hz, 1 H, H-15), 4.77 (d, J = 2.1 Hz, 1 H, H-1′), 4.67 (d, J = 14.6 Hz, 1 H, H_A-8a), 4.58 (d, J = 14.6 Hz, 1 H, H_B-8a), 4.44 (br. s, 1 H, H-5), 4.21 (s, 1 H, HO-7), 3.94 (br. s, 1 H, H-13), 3.87–3.57 (m, 4 H, H-3′, H-5′, H-3′′ and H-5′′), 3.82 (d, J = 5.6 Hz, 1 H, H-6), 3.43 (s, 3 H, OMe), 3.40–3.30 (m, 2 H, H-2 and H-17), 3.34 (s, 3 H, OMe), 3.25–3.18 (m, 2 H, H-25, H-4′ or H-4′′), 3.14 (t, J = 8.8 Hz, 1 H, H-4′′ or H-4′), 2.51 (m, 1 H, H-12), 2.38–2.18 (m, 4 H, H_2-16, H_{eq}-2′ and H_{eq}-2′′), 1.98 (dd, J = 4.4, 12.0 Hz, 1 H, H_{eq}-20), 1.79 (br. s, 3 H, Me-4), 1.75 (br. d, J = 12.0 Hz, 1 H, H_{eq}-18), 1.66 (br. d, J = 11.4 Hz, 1 H), 1.60–1.30 (m, 10 H, including H_2-22, H_2-23, H_2-27), 1.51 (br. s, 3 H, Me-14), 1.37 (q, J = 12.0 Hz, 1 H, H_{ax}-18), 1.26 (d, J = 6.0 Hz, 3 H, Me-5′), 1.21 (d, J = 6.0 Hz, 3 H, Me-5′′), 1.16 (d, J = 6.8 Hz, 3 H, Me-12), 0.95–0.80 (m, 6 H, Me-24 and Me-27), 0.93 (s, 9 H, Me_3CSi), 0.89 (s, 9 H, Me_3CQi), 0.78 (d, J = 4.0 Hz, 3 H, Me-26), 0.14 (s, 6 H, Me_2Si), 0.10 (s, 6 H, Me_2Si) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 174.1 (C-1), 140.2 (C-8), 137.5 (C-4 and C-11), 135.0 (C-14), 124.8 (C-10), 119.3 (C-9), 118.3 (C-15), 117.3 (C-3), 98.6 (C-1′′), 97.5 (C-21), 94.8 (C-1′), 81.9 (C-13), 80.8 (C-7), 80.2 (C-4′), 80.0 (C-6), 79.3 (C-3′ and C-3′′), 78.5 (C-4′′), 76.6 (C-25), 69.5 (C-5), 69.0 (C-5′′), 68.7 (C-19), 67.9 (C-8a), 67.3 (C-17 or C-5′), 67.2 (C-5′ or C-17), 56.6, 56.3 (2 OMe), 45.8 (C-2), 41.2 (C-20), 39.6 (C-12), 36.8 (C-18), 35.7 (C-22), 35.4 (C-26), 34.6 (C-2′ and C-2′′), 34.1 (C-16), 31.2 (C-24), 28.1 (C-23), 27.3 (C-27), 26.0 (*Me*$_3$CSi-4′′), 25.8 (*Me*$_3$CSi-5), 20.3 (Me-12), 20.0 (Me-4), 18.3 (Me-5′ and Me$_3$*C*Si-5), 18.1 (Me$_3$*C*Si-4′′), 17.9 (Me-5′′), 17.4 (Me-24), 15.1 (Me-14), 12.4 (Me-26), 12.1 (Me-27), –4.9, –4.8, –4.6, –4.0 (2 Me_2Si) ppm. HRMS (ESI, MeOH): *m*/*z* calcd. for $C_{60}H_{102}O_{14}NaSi_2$ [M + Na]$^+$ 1125.67059; found 1125.6717.

5-*O*-(*tert*-Butyldimethylsilyl) Ivermectin (2): $[\alpha]_D$ = +33.1 (*c* = 0.72, $CHCl_3$). M.p. 136–142 °C. IR (KBr): $\tilde{\nu}$ = 3479, 3000–2850, 1714, 1461, 1379, 1252, 1200–1000, 987, 872, 837, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (app dt, J = 2.3, 8.6 Hz, 1 H, H-9), 5.77–5.66 (m, 2 H, H-10 and H-11), 5.40 (d, J = 3.2 Hz, 1 H, H-1′′), 5.38–5.25 (m, 2 H, H-3 and H-19), 4.98 (br. d, J = 10.4 Hz, 1 H, H-15), 4.78 (d, J = 3.2 Hz, 1 H, H-1′), 4.68 (dd, J = 2.3, 14.6 Hz, 1 H, H_A-8a), 4.59 (dd, J = 2.3, 14.6 Hz, 1 H, H_B-8a), 4.44 (m, 1 H, H-5), 4.23 (br. s, 1 H, HO-7), 3.94 (br. s, 1 H, H-13), 3.88–3.59 (m, 4 H, H-3′, H-5′, H-3′′ and H-5′′), 3.82 (d, J = 5.6 Hz, 1 H, H-6), 3.48 (m, 1 H, H-17), 3.43 (s, 3 H, OMe), 3.42 (s, 3 H, OMe), 3.39 (sext, J = 2.4 Hz, 1 H, H-2), 3.24 (t, J = 9.1 Hz, 1 H, H-4′ or H-4′′), 3.21 (app d, J = 7.6 Hz, 1 H, H-25), 3.17 (t, J = 9.1 Hz, 1 H, H-4′′ or H-4′), 2.52 (m, 2 H, H-12 and HO-4′′), 2.38–2.18 (m, 4 H, H_2-16. H_{eq}-2′ and H_{eq}-2′′), 1.99 (dd, J = 4.0, 12.8 Hz, 1 H, H_{eq}-20), 1.79 (br. s, 3 H, Me-4), 1.75 (br. d, J = 12.2 Hz, 1 H, H_{eq}-18), 1.65 (br. d, J = 10.8 Hz, 1 H), 1.60–1.32 (m, 10 H, including H_2-22, H_2-23, H_2-27), 1.51 (br. s, 3 H, Me-14), 1.37 (q, J = 12.2 Hz, 1 H, H_{ax}-18), 1.28 (d, J = 6.3 Hz, 3 H, Me-5′′), 1.26 (d, J = 6.3 Hz, 3 H, Me-5′), 1.16 (d, J = 7.1 Hz, 1 H, Me-12), 0.93 (s, 9 H, Me_3CSi), 0.93 (app t, 3 H, Me-27), 0.86 (d, J = 6.8 Hz, 3 H, Me-24), 0.79 (d, J = 5.2 Hz, 3 H, Me-26), 0.14 (s, 6 H, Me_2Si) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 174.0 (C-1), 140.2 (C-8), 137.5 (C-4 and C-11), 135.0 (C-14), 124.8 (C-10), 119.3 (C-9), 118.3 (C-15), 117.3 (C-3), 98.5 (C-1′′), 97.5 (C-21), 94.8 (C-1′), 81.8 (C-13), 80.4 (C-7), 80.2 (C-4′), 80.1 (C-6), 79.3 (C-3′), 78.2 (C-3′′), 76.6 (C-25), 76.0 (C-4′′), 69.5 (C-5), 68.7 (C-19), 68.1 (C-5′′), 67.9 (C-8a), 67.2 (C-5′ and C-17), 56.4 (2 OMe), 45.7 (C-2), 41.1 (C-20), 39.6 (C-12), 36.8 (C-18), 35.7 (C-22), 35.4 (C-26), 34.5 (C-2′), 34.1 (C-2′′ and C-16), 31.2 (C-24), 28.0 (C-23), 27.2 (C-27), 25.8 (*Me*$_3$CSi), 20.2 (Me-12), 20.0 (Me-4), 18.4 (C6′ and Me$_3$*C*Si), 17.6 (Me-5′′), 17.4 (Me-24), 15.1 (Me-14), 12.4 (Me-26), 12.0 (Me-27), –4.9, –4.7 (Me_2Si) ppm. HRMS (ESI, MeOH): *m*/*z* calcd. for $C_{54}H_{88}O_{14}NaSi$ [M + Na]$^+$ 1011.58411; found 1011.5843.

General Procedure for Macrolactone Opening: An oven-dried 25-mL flask was charged under nitrogen with the required starting IVM derivative, the chosen alcohol (10.0 equiv.) and [Ti(O*i*Pr)$_4$] or [Ti(OEt)$_4$] (1.0–1.5 equiv.). The reaction mixture was heated to 90–110 °C for 3–7 h under nitrogen and monitored by TLC. After cooling to room temperature, the mixture was extracted according to one of the two following processes:

Solid-Phase Work-up: The reaction mixture was diluted with light petroleum ether and poured over a pad of silica. Elution with hexane/AcOEt mixtures (from 100:0 to 0:100) gave a mixture of the required secoester and recovered starting material.

Liquid-Phase Work-up: The reaction mixture was diluted with diethyl ether or chloroform, and the combined organic layers were washed with aqueous 0.5 N HCl (3×). The aqueous phase was re-extracted with diethyl ether or chloroform (2×), and the combined organic extracts were washed with brine (2×), dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

After evaporation of the solvent, the crude product was purified by flash-chromatography on silica gel to give the required secoester as well as unreacted starting material.

Some representative experiments are described below.

Ivermectin Ethyl Secoester (Et-4): Ivermectin **1** (1.75 g, 2.0 mmol), ethanol (1.20 mL, 20.5 mmol, 10.2 equiv.) and [Ti(OEt)$_4$] (0.65 mL, 3.1 mmol, 1.5 equiv.) were treated according to the general procedure at 110 °C for 6–7 h. The reaction mixture was extracted with chloroform as described above to give, after purification by chromatography on silica gel (hexane/AcOEt mixtures, from 50:50 to 0:100; then AcOEt/MeOH, from 100:0 to 80:20), 0.18 g (10.0%) of recovered **1** and 1.25 g (68%) of **Et-4** as a pale-yellow foam. $[a]_D$ = –24.8 (c = 0.97, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3436, 3000–2850, 1733, 1455, 1382, 1150–1000, 986 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08 (dt, J = 2.2, 9.6 Hz, 1 H, H-9), 5.91 (dd, J = 9.6, 15.2 Hz, 1 H, H-10), 5.85 (dd, J = 6.4, 15.2 Hz, 1 H, H-11), 5.47–5.38 (m, 2 H, H-3 and H-15), 5.27 (br. d, J = 3.2 Hz, 1 H, H-1′′), 4.74 (br. d, J = 2.8 Hz, 1 H, H-1′), 4.70 (dd, J = 2.2, 14.0 Hz, 1 H, H$_A$-8a), 4.62 (dd, J = 2.2, 14.0 Hz, 1 H, H$_B$-8a), 4.41 (dd, J = 1.1, 5.5 Hz, 1 H, H-5), 4.25–4.15 (m, 2 H, COO*CH*2CH$_3$), 4.16 (d, J = 5.5 Hz, 1 H, H-6), 4.06 (m, 1 H, H-19), 3.77–3.35 (m, 6 H, H-2, H-17, H-3′, H-5′, H-3′′ and H-5′′), 3.64 (d, J = 8.4 Hz, 1 H, H-13), 3.41 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 3.17–3.09 (m, 3 H, H-25, H-4′ and H-4′′), 2.46 (m, 1 H, H-12), 2.33–2.25 (m, 3 H, H$_2$-16, H$_{eq}$-2′ or H$_{eq}$-2′′), 2.11 (dd, J = 5.0, 12.6 Hz, 1 H, H$_{eq}$-2′′ or H$_{eq}$-2′), 1.96 (ddd, J = 1.2, 4.4, 12.1 Hz, 1 H, H$_{eq}$-20), 1.90 (br. d, J = 11.8 Hz, 1 H, H$_{eq}$-18), 1.83 (s, 3 H, Me-4), 1.64 (br. d, J = 10.1 Hz, 1 H), 1.54 (br. s, 3 H, Me-14), 1.52–1.46 (m, 6 H, H$_2$-22, H$_2$-23 and H$_2$-27), 1.35–1.23 (m, 11 H, including Me-5′ or Me-5′′, COOCH$_2$*CH$_3$*), 1.16 (d, J = 6.0 Hz, 3 H, Me-5′′ or Me-5′), 1.10 (q, J = 11.8 Hz, 1 H, H$_{ax}$-18), 0.91 (d, J = 6.8 Hz, 3 H, Me-12), 0.89 (t, J = 7.2 Hz, 3 H, Me-27), 0.81 (d, J = 6.8 Hz, 3 H, Me-24), 0.78 (d, J = 5.6 Hz, 3 H, Me-26) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 173.2 (C-1), 142.5 (C-8), 140.1 (C-11), 138.7 (C-4), 133.7 (C-14), 127.1 (C-10), 125.1 (C-15), 120.5 (C-9), 117.3 (C-3), 99.2 (C-1′′), 97.3 (C-21), 93.2 (C-1′), 86.2 (C-13), 82.9 (C-6), 82.1 (C-4′), 79.3 (C-3′), 78.4 (C-3′′), 77.9 (C-7), 77.2 (C-25), 76.0 (C-4′′), 68.8 (C-8a), 68.2 (C-5′′), 67.7 (C-5), 67.6 (C-17), 66.8 (C-5′), 64.8 (C-19), 61.4 (COO*CH$_2$*CH$_3$), 56.3, 56.0 (2 OMe), 47.4 (C-2), 45.0 (C-20), 40.5 (C-18), 38.4 (C-12), 35.8 (C-22), 35.4 (C-26), 34.8 (C-2′), 34.4 (C-2′′), 34.1 (C-16), 31.3 (C-24), 28.1 (C-23), 27.5 (C-27), 19.2 (Me-4), 18.2 (Me-12), 17.6 (Me-5′′), 17.4 (Me-5′), 16.6 (Me-24), 14.0 (COOCH$_2$*CH$_3$*), 12.4 (Me-26), 11.4 (Me-27), 11.3 (Me-14) ppm. HRMS (ESI, MeOH): m/z calcd. for $C_{50}H_{80}O_{15}Na$ [M + Na]$^+$ 943.53949; found 943.5391.

5-*O*-(*tert*-Butyldimethylsilyl) Ivermectin Ethyl Secoester (Et-5): Mono-silylated Ivermectin **2** (8.14 g, 8.2 mmol), ethanol (4.81 mL, 82.1 mmol, 10.0 equiv.) and [Ti(OEt)$_4$] (1.71 mL, 8.2 mmol, 1.0 equiv.) were treated according to the general procedure at 90 °C for 3–4 h. The reaction mixture was extracted with diethyl ether as described above to give, after purification by chromatography on silica gel (hexane/AcOEt mixtures, from 90:10 to 40:60), 5.03 g (59%) of **Et-5** as a pale-yellow foam. $[a]_D$ = –53.9 (c = 0.98, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3483, 3000–2850, 1736, 1718, 1462, 1383, 1257, 1200–1000, 986, 872, 837, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (m, 1 H, H-9), 5.93 (m, 2 H, H-10 and H-11), 5.42 (br. t, J = 7.2 Hz, 1 H, H-15), 5.38 (m, 1 H, H-3), 5.29 (d, J = 3.2 Hz, 1 H, H-1′′), 4.93 (br. s, 1 H, HO-7), 4.74 (d, J = 2.8 Hz, 1 H, H-1′), 4.69 (dd, J = 2.2, 14.2 Hz, 1 H, H$_A$-8a), 4.65 (dd, J = 2.2, 14.2 Hz, 1 H, H$_B$-8a), 4.51 (br. d, J = 4.8 Hz, 1 H, H-5), 4.20 (m, 2 H, COO*CH$_2$*CH$_3$), 4.05 (m, 1 H, H-19), 3.87 (d, J = 4.8 Hz, 1 H, H-6), 3.76–3.51 (m, 4 H, H-3′, H-5′, H-3′′ and H-5′′), 3.65 (d, J = 8.0 Hz, 1 H, H-13), 3.46. (m, 1 H, H-17), 3.43 (s, 3 H, OMe), 3.38 (m, 1 H, H-2), 3.37 (s, 3 H, OMe), 3.15 (t, J = 9.2 Hz, 1 H, H-4′ or H-4′′), 3.11 (t, J = 9.2 Hz, 1 H, H-4′′ or H-4′), 3.11 (br. d, 1 H, H-25), 2.59 (br. s, 1 H, HO-4′′), 2.47 (m, 1 H, H-12), 2.34–2.18 (m, 3 H, H$_2$-16 and H$_{eq}$-2′′), 2.12 (dd, J = 5.2, 12.0 Hz, 1 H, H$_{eq}$-2′), 1.96 (ddd, J = 1.6, 4.8, 12.0 Hz, 1 H, H$_{eq}$-20), 1.91 (br. d, J = 11.8 Hz, 1 H, H$_{eq}$-18), 1.80 (br. s, 3 H, Me-4), 1.70 (br. s, 1 H, HO-19), 1.63 (br. d, J = 10.6 Hz, 1 H), 1.55 (s, 3 H, Me-14), 1.53–1.45 (m, 6 H, H$_2$-22, H$_2$-23, H$_2$-27), 1.36–1.19 (m, 4 H), 1.29 (t, J = 7.2 Hz, 3 H, COOCH$_2$*CH$_3$*), 1.26 (d, J = 6.4 Hz, 3 H, Me-5′), 1.17 (d, J = 6.4 Hz, 3 H, Me-5′′), 1.10 (q, J = 11.8 Hz, 1 H, H$_{ax}$-18), 0.92 (s, 9 H, Me$_3$CSi), 0.92 (d, J = 6.8 Hz, 3 H, Me-12), 0.89 (t, J = 7.6 Hz, 3 H, Me-27), 0.81 (d, J = 6.8 Hz, 3 H, Me-24), 0.78 (d, J = 6.0 Hz, 3 H, Me-26), 0.13 (s, 6 H, Me$_2$Si) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 173.7 (C-1), 142.9 (C-8), 139.4 (C-11), 137.7 (C-4), 133.8 (C-14), 127.0 (C-10), 124.9 (C-15), 119.6 (C-9), 117.3 (C-3), 99.1 (C-1′′), 97.3 (C-21), 93.3 (C-1′), 86.1 (C-13), 82.8 (C-6), 81.8 (C-4′), 79.4 (C-3′), 78.5 (C-3′′), 78.0 (C-7), 77.3 (C-25), 76.3 (C-4′′), 69.1 (C-5), 68.4 (2C, C-5′′ and C-8a), 67.7 (C-17), 66.8 (C-5′), 64.9 (C-19), 61.4 (COO*CH$_2$*CH$_3$), 56.5, 56.4 (2 OMe), 46.6 (C-2), 45.1 (C-20), 40.6 (C-18), 38.5 (C-12), 35.9 (C-22), 35.5 (C-26), 34.8 (C-2′′), 34.6 (C-2′), 34.1 (C-16), 31.4 (C-24), 28.1 (C-23), 27.5 (C-27), 25.8 (*Me$_3$*CSi), 19.8 (Me-4), 18.2 (Me-12 and Me$_3$*C*Si), 17.6 (Me-5′′), 17.4 (Me-5′), 16.3 (Me-24), 14.1 (COOCH$_2$*CH$_3$*), 12.5 (Me-26), 11.5 (Me-14 and Me-27), –5.0, –4.6 (Me$_2$Si) ppm. HRMS (ESI, MeOH): m/z calcd. for $C_{56}H_{94}O_{15}NaSi$ [M + Na]$^+$ 1057.62597; found 1057.6256.

4′′,5-Bis-*O*-(*tert*-Butyldimethylsilyl) Ivermectin Ethyl Secoester (Et-6): Bis-silylated Ivermectin **3** (4.43 g, 4.01 mmol), ethanol (2.35 mL, 40.10 mmol, 10.0 equiv.) and [Ti(OEt)$_4$] (0.84 ml, 4.01 mmol, 1.0 equiv.) were treated according to the general procedure at 90 °C for 3–4 h. The reaction mixture was extracted with diethyl ether as described above to give, after purification by chromatography on silica gel (hexane/AcOEt mixtures, from 80:20 to 70:30), 2.43 g (53%) of 4′′,5-*O*-bis(*tert*-butyldimethylsilyl) Ivermectin ethyl secoester (**Et-6**) as a yellow powder. In another experiment starting from **3** (6.59 g, 6.0 mmol), 3.93 g (57%) of **Et-6** was obtained. $[a]_D$ = –55.8 (c = 0.90, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3491, 3000–2850, 1736, 1716, 1473, 1464, 1387, 1256, 1150–1000, 986, 872, 837, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08 (m, 1 H, H-9), 5.91–5.80 (m, 2 H, H-10 and H-11), 5.42–5.36 (m, 2 H, H-3 and H-15), 5.33 (br. d, J = 3.6 Hz, 1 H, H-1′′), 4.74 (br. d, J = 3.2 Hz, 1 H, H-1′), 4.65 (br. s, 3 H, H$_2$-8a and HO-7), 4.51 (br. s, 1 H, H-5), 4.20 (q, J = 7.2 Hz, 2 H, COO*CH$_2$*CH$_3$), 4.03 (m, 1 H, H-19), 3.90 (d, J = 4.8 Hz, 1 H, H-6), 3.76 (d, J = 6.8 Hz, 1 H, H-13), 3.73–3.50 (m, 4 H, H-3′, H-5′, H-3′′ and H-5′′), 3.42 (app sext, J = 2.3 Hz, 1 H, H-2), 3.36 (s, 3 H, OMe), 3.32 (s, 3 H, OMe), 3.34–3.29 (m, 1 H, H-17), 3.19 (t, J = 8.8 Hz, 1 H, H-4′ or H-4′′), 3.13 (t, J = 8.8 Hz, 1 H, H-4′′ or H-4′), 3.12 (br. d, 1 H, H-25), 2.47 (m, 1 H, H-12), 2.35–2.16 (m, 3 H, H$_2$-16 and H$_{eq}$-2′′), 2.13 (dd, J = 5.2, 12.0 Hz, 1 H, H$_{eq}$-2′), 1.95 (dd, J = 4.8, 12.2 Hz, 1 H, H$_{eq}$-20), 1.89 (br. d, J = 11.9 Hz, 1 H, H$_{eq}$-18), 1.80 (br. s, 3 H, Me-4), 1.68 (br. s, 1 H, HO-19), 1.63 (br. d, J = 10.2 Hz, 1 H), 1.54 (s, 3 H, Me-14), 1.53–1.46 (m, 6 H, H$_2$-22, H$_2$-23, H$_2$-27), 1.36–1.24 (m, 4 H), 1.29 (t, J = 7.2 Hz, 3 H, COOCH$_2$*CH$_3$*), 1.22 (d, J = 6.4 Hz, 3 H, Me-5′), 1.21 (d, J = 6.4 Hz, 3 H, Me-5′′), 1.09 (q, J = 11.9 Hz, 1 H, H$_{ax}$-18), 0.97 (d, J = 6.8 Hz, 3 H, Me-12), 0.92 (s, 9 H, Me$_3$CSi), 0.90 (t, J = 7.6 Hz, 3 H, Me-27), 0.89 (s, 9 H, Me$_3$CSi), 0.81 (d, J = 6.8 Hz, 3 H, Me-24), 0.78 (d, J = 6.0 Hz, 3 H, Me-26), 0.12 (s, 6 H, Me$_2$Si-5), 0.09, 0.07 (2s, 6 H, Me$_2$Si-4′′) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 173.5 (C-1), 142.9 (C-8), 138.9 (C-11), 137.8 (C-4), 133.9 (C-14), 126.3 (C-10), 124.9 (C-15), 119.7 (C-9), 117.4 (C-3), 98.3 (C-1′′), 97.2 (C-21), 93.5 (C-1′),

85.1 (C-13), 83.1 (C-6), 80.5 (C-4′), 79.4 (C-3′), 78.6 (C-3′′), 78.4 (C-7), 77.2 (C-25), 77.1 (C-4′′), 69.2 (C-5), 68.9 (C-5′′), 68.5 (C-8a), 67.7 (C-17), 67.1 (C-5′), 64.8 (C-19), 61.2 (COO*CH*$_2$CH$_3$), 56.3 56.3 (2 OMe), 46.8 (C-2), 45.0 (C-20), 40.5 (C-18), 39.2 (C-12), 35.8 (C-22), 35.4 (C-26), 34.9 (C-2′′), 34.6 (C-2′), 34.0 (C-16), 31.3 (C-24), 28.1 (C-23), 27.5 (C-27), 26.0 (4′′-*Me*$_3$CSi), 25.8 (5-*Me*$_3$CSi), 19.8 (Me-4),‘18.3 (Me-5′′, Me-12, Me$_3$*C*Si-4′′ and Me$_3$*C*Si-5), 17.4 (Me-5′), 16.5 (Me-24), 14.1 (COOCH$_2$*CH*$_3$), 12.4 (Me-26), 12.0 (Me-27), 11.5 (Me-14), –5.0, –4.8, –4.6, –4.0 (2 Me$_2$Si) ppm. HRMS (ESI, MeOH): *m*/*z* calcd. for $C_{62}H_{108}O_{15}NaSi_2$ $[M + Na]^+$ 1171.71245; found 1171.7134.

5-*O*-(*tert*-Butyldimethylsilyl) Ivermectin Isoamyl Secoester (*i*Amyl-5): Mono-protected Ivermectin **2** (4.93 g, 5.0 mmol), isoamyl alcohol (5.50 mL, 50.5 mmol, 10.0 equiv.) and [Ti(O*i*Pr)$_4$] (1.50 mL, 5.1 mmol, 1.0 equiv.) were treated according to the general procedure at 110 °C for 4–5 h. The reaction mixture was extracted following the solid-phase procedure described above to give, after purification by chromatography on silica gel (hexane/AcOEt mixtures, from 100:0 to 30:70), 3.21 g (60%) of ***i*Amyl-5** as a pale-yellow foam. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 173.8 (C-1), 142.9 (C-8), 139.4 (C-11), 137.8 (C-4), 133.8 (C-14), 127.0 (C-10), 124.9 (C-15), 119.6 (C-9), 117.2 (C-3), 99.1 (C-1′′), 97.3 (C-21), 93.3 (C-1′), 86.1 (C-13), 82.8 (C-6), 81.8 (C-4′), 79.4 (C-3′), 78.4 (C-3′′), 78.0 (C-7), 77.3 (C-4′′ and C-25), 69.1 (C-5), 68.4 (C-5′′ and C-8a), 67.7 (C-17), 66.8 (C-5′), 65.5 (COO*CH*$_2$CH$_2$CHMe$_2$), 64.8 (C-19), 56.5, 56.3 (2 OMe), 46.8 (C-2), 45.1 (C-20), 40.6 (C-18), 38.4 (C-12), 35.9 (C-22), 35.5 (C-26), 34.7 (C-2′ and C-2′′), 34.1 (C-16), 31.3 (C-24), 28.1 (C-23), 27.9 (COOCH$_2$CH$_2$CH*Me$_2$*), 27.5 (C-27), 25.8 (*Me*$_3$CSi), 22.2 (COOCH$_2$*CH*$_2$CHMe$_2$), 19.8 (Me-4), 18.3 (Me$_3$*C*Si), 18.2 (Me-12), 17.6 (Me-5′′), 17.4 (Me-5′), 16.3 (Me-24), 13.9 (COOCH$_2$CH$_2$*CH*Me$_2$), 12.4 (Me-26), 11.5 (Me-14 and Me-27), –5.0, –4.6 (Me$_2$Si) ppm.

5-*O*-(*tert*-Butyldimethylsilyl) Ivermectin β-(Trimethylsilyl)ethyl Secoester (TSE-5): Mono-protected Ivermectin **2** (1.97 g, 2.0 mmol), β-trimethylsilyl ethanol (2.86 mL, 20.0 mmol, 10.0 equiv.) and [Ti(O*i*Pr)$_4$] (0.60 mL, 2.0 mmol, 1.0 equiv.) were treated according to the general procedure at 110 °C for 5–6 h. The reaction mixture was extracted following the solid-phase procedure described above to give, after purification by chromatography on silica gel (hexane/AcOEt mixtures, from 100:0 to 40:60), 0.12 g (5.9%) of **2** and 1.00 g (45.4%) of **TSE-5** as a yellow foam. $[\alpha]_D$ = –45.7 (*c* = 0.74, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3469, 3000–2850, 1732, 1713, 1383, 1252, 1150–1000, 986, 861, 837, 776 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (br. d, 1 H, H-9), 5.89 (m, 2 H, H-10 and H-11), 5.42 (br. t, *J* = 7.1 Hz, 1 H, H-15), 5.38 (br. s, 1 H, H-3), 5.29 (d, *J* = 3.5 Hz, 1 H, H-1′′), 4.74 (d, *J* = 3.0 Hz, 1 H, H-1′), 4.69 (br. d, *J* = 2.2, 14.5 Hz, 1 H, H$_A$-8a), 4.64 (br. d, *J* = 2.2, 14.5 Hz, 1 H, H$_B$-8a), 4.51 (br. s, 1 H, H-5), 4.22 (m, 2 H, COO*CH*$_2$CH$_2$SiMe$_3$), 4.05 (m, 1 H, H-19), 3.87 (d, *J* = 4.8 Hz, 1 H, H-6), 3.76–3.35 (m, 6 H, H-2, H-17, H-3′, H-5′, H-3′′ and H-5′′), 3.65 (d, *J* = 7.8 Hz, 1 H, H-13), 3.43 (s, 3 H, OMe), 3.38 (s, 3 H, OMe), 3.20–3.05 (m, 3 H, H-4′, H-4′′ and 25), 2.47 (m, 1 H, H-12), 2.33–2.22 (m, 3 H, H$_2$-16 and H$_{eq}$-2′′), 2.12 (dd, *J* = 5.1, 12.9 Hz, 1 H, H$_{eq}$-2′), 2.00–1.85 (m, 2 H, H$_{eq}$-18 and H$_{eq}$-20), 1.80 (br. s, 3 H, Me-4), 1.64 (br. d, *J* = 10.3 Hz, 1 H), 1.55 (s, 3 H, Me-14), 1.53–1.46 (m, 6 H, H$_2$-22, H$_2$-23, H$_2$-27), 1.35–1.20 (m, 4 H), 1.26 (d, *J* = 6.1 Hz, 3 H, Me-5′′), 1.16 (d, *J* = 6.1 Hz, 3 H, Me-5′), 1.10 (q, *J* = 11.4 Hz, 1 H, H$_{ax}$-18), 1.02 (m, 2 H, COOCH$_2$*CH*$_2$SiMe$_3$), 0.94–0.84 (m, 6 H, Me-12 and Me-27), 0.92 (s, 9 H, Me$_3$CSi), 0.81 (d, *J* = 6.8 Hz, 3 H, Me-24), 0.78 (d, *J* = 5.6 Hz, 3 H, Me-26), 0.13 (s, 6 H, Me$_2$Si), 0.04 (s, 9 H, COOCH$_2$CH$_2$Si*Me$_3$*) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 174.0 (C-1), 142.9 (C-8), 139.4 (C-11), 137.7 (C-4), 133.9 (C-14), 127.0 (C-10), 124.8 (C-15), 119.6 (C-9), 117.2 (C-3), 99.2 (C-1′′), 97.3 (C-21), 93.3 (C-1′), 86.1 (C-13), 82.6 (C-6), 81.8 (C-4′), 79.4 (C-3′), 78.5 (C-3′′), 78.1 (C-7), 77.3 (C-25), 76.3 (C-4′′), 25), 69.0 (C-5), 68.5 (C-8a), 68.4 (C-5′′), 67.7 (C-17), 66.8 (C-5′), 64.9 (C-19), 63.8 (COO*CH*$_2$CH$_2$SiMe$_3$), 56.6 (OMe), 56.4 (OMe), 46.6 (C-2), 45.1 (C-20), 40.6 (C-18), 38.4 (C-12), 35.9 (C-22), 35.5 (C-26), 34.8 (C-2′′), 34.7 (C-2′), 34.1 (C-16), 31.3 (C-24), 28.1 (C-23), 27.6 (C-27), 25.8 (*Me*$_3$CSi-5), 19.8 (Me-4), 18.3 (Me$_3$*C*Si-5), 18.2 (Me-12), 17.7 (C-6′′), 17.4 (C-6′), 17.3 (COOCH$_2$*CH*2SiMe$_3$), 16.2 (Me-24), 12.5 (Me-26), 11.5 (2C, Me-14 and C-28), –1.6 (COOCH$_2$CH$_2$Si*Me$_3$*), –5.0, –4.6 (Me$_2$Si-5) ppm. HRMS (ESI, MeOH): *m*/*z* calcd. for $C_{59}H_{102}O_{15}NaSi_2$ $[M + Na]^+$ 1129.66550; found 1129.6647.

5-*O*-(*tert*-Butyldimethylsilyl) Ivermectin Methyl Secoester (Me-5): Mono-protected Ivermectin **2** (1.92 g, 1.94 mmol), methanol (0.80 mL, 19.78 mmol, 10.2 equiv.) and [Ti(O*i*Pr)$_4$] (0.60 mL, 2.0 mmol, 1.0 equiv.) were treated according to the general procedure at 110 °C for 5–6 h. The reaction mixture was extracted following the solid-phase procedure described above to give, after purification by chromatography on silica gel (hexane/AcOEt mixtures, from 100:0 to 20:80), 0.16 g (8.2%) of recovered **2**, 0.28 g (14%) of 5-*O*-(*tert*-butyldimethylsilyl) Ivermectin isopropyl secoester ***i*Pr-5** (pale-yellow foam), and 1.07 g (53.8%) of the expected methyl secoester **Me-5** (pale-yellow foam).

5-O-(*tert*-Butyldimethylsilyl) Ivermectin isopropyl secoester (*i*Pr-5): $[\alpha]_D$ = –27.5 (*c* = 0.73, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3462, 3000–2850, 1732, 1716, 1456, 1381, 1252, 1150–1000, 985, 870, 837, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (br. d, 1 H, H-9), 5.89 (br. d, 2 H, H-10 and H-11), 5.42 (br. t, *J* = 7.2 Hz, 1 H, H-15), 5.36 (br. s, 1 H, H-3), 5.29 (d, *J* = 3.2 Hz, 1 H, H-1′′), 5.06 (m, 1 H, COO*CH*Me$_2$), 5.02 (br. s, 1 H, HO-7), 4.73 (d, *J* = 3.2 Hz, 1 H, H-1′), 4.70 (br. d, *J* = 14.2 Hz, 1 H, H$_A$-8a), 4.64 (br. d, *J* = 14.2 Hz, 1 H, H$_B$-8a), 4.51 (br. s, 1 H, H-5), 4.05 (m, 1 H, H-19), 3.86 (d, *J* = 4.8 Hz, 1 H, H-6), 3.76–3.30 (m, 6 H, H-2, H-17, H-3′, H-5′, H-3′′ and H-5′′), 3.65 (d, *J* = 8.8 Hz, 1 H, H-13), 3.43 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 3.18–3.08 (m, 3 H, H-4′, H-4′′ and H-25), 2.60 (br. s, 1 H, HO-4′′), 2.47 (m, 1 H, H-12), 2.34–2.22 (m, 3 H, H$_2$-16 and H$_{eq}$-2′′), 2.12 (dd, *J* = 4.9, 13.5 Hz, 1 H, H$_{eq}$-2′), 1.98–1.88 (m, 2 H, H$_{eq}$-18 and H$_{eq}$-20), 1.80 (br. s, 3 H, Me-4), 1.70 (br. s, 1 H, HO-19), 1.64 (br. d, *J* = 10.4 Hz, 1 H), 1.55 (s, 3 H, Me-14), 1.53–1.45 (m, 6 H, H$_2$-22, H$_2$-23, H$_2$-27), 1.34–1.22 (m, 13 H, including Me-5′′ and COOCH*Me$_2$*), 1.17 (d, *J* = 6.0 Hz, 3 H, Me-5′), 1.10 (q, *J* = 11.2 Hz, 1 H, H$_{ax}$-18), 0.95–0.85 (m, 6 H, Me-12 and Me-27), 0.92 (s, 9 H, Me$_3$CSi), 0.81 (d, *J* = 6.8 Hz, 3 H, Me-24), 0.78 (d, *J* = 5.2 Hz, 3 H, Me-26), 0.13 (s, 6 H, Me$_2$Si) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 173.3 (C-1), 142.9 (C-8), 139.3 (C-11), 137.5 (C-4), 133.8 (C-14), 127.0 (C-10), 124.9 (C-15), 119.6 (C-9), 117.3 (C-3), 99.1 (C-1′′), 97.2 (C-21), 93.2 (C-1′), 86.0 (C-13), 82.7 (C-6), 81.8 (C-4′), 79.4 (C-3′), 78.4 (C-3′′), 78.0 (C-7), 77.3 (C-25), 76.3 (C-4′′), 69.1 (C-5), 69.0 (COO*CH*Me$_2$), 68.4 (2C, C-5′′ and C-8a), 67.7 (C-17), 66.8 (C-5′), 64.8 (C-19), 56.5 (OMe), 56.5, 56.3 (2 OMe), 46.6 (C-2), 45.0 (C-20), 40.6 (C-18), 38.4 (C-12), 35.8 (C-22), 35.4 (C-26), 34.7 (C-2′ and C-2′′), 34.1 (C-16), 28.1 (C-23), 27.5 (C-27), 25.8 (*Me*$_3$CSi), 21.6 and 21.7 (COOCH*Me$_2$*), 19.8 (Me-4), 18.3 (Me-12 and Me$_3$*C*Si), 17.6 (Me-5′′), 17.6 (Me-5′′), 17.4 (Me-5′), 16.3 (Me-24), 12.4 (Me-26), 11.4 (Me-14 and Me-27), –5.0, –4.6 (Me$_2$Si) ppm.

5-O-(*tert*-Butyldimethylsilyl) Ivermectin Methyl Secoester (Me-5): $[\alpha]_D$ = –48.8 (*c* = 0.90, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3473, 3000–2850, 1741, 1456, 1383, 1257, 1150–1000, 985, 864, 837, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06 (br. s, 1 H, H-9), 5.89 (br. d, 2 H, H-10 and H-11), 5.42 (br. t, *J* = 7.1 Hz, 1 H, H-15), 5.39 (br. s, 1 H, H-3), 5.30 (d, *J* = 2.0 Hz, 1 H, H-1′′), 4.78 (br. s, 1 H, HO-7), 4.74 (br. s, 1 H, H-1′), 4.68 (br. d, *J* = 14.5 Hz, 1 H, H$_A$-8a),

4.65 (br. d, J = 14.5 Hz 1 H, H_B-8a), 4.51 (br. s, 1 H, H-5), 4.05 (m, 1 H, H-19), 3.88 (d, J = 4.8 Hz, 1 H, H-6), 3.72–3.40 (m, 6 H, H-2, H-17, H-3′, H-5′, H-3′′ and H-5′′), 3.74 (s, 3 H, COOMe), 3.65 (d, J = 8.0 Hz, 1 H, H-13), 3.42 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 3.20–3.05 (m, 3 H, H-4′, H-4′′ and H-25), 2.60 (br. s, 1 H, HO-4′′), 2.47 (m, 1 H, H-12), 2.35–2.20 (m, 3 H, H_2-16 and H_{eq}-2′′), 2.12 (dd, J = 5.2, 12.0 Hz, 1 H, H_{eq}-2′), 2.00–1.88 (m, 2 H, H_{eq}-18 and H_{eq}-20), 1.80 (br. s, 3 H, Me-4), 1.72 (br. s, 1 H, HO-19), 1.64 (br. s, J = 10.3 Hz, 1 H), 1.55 (s, 3 H, Me-14), 1.55–1.40 (m, 6 H, H_2-22, H_2-23, H_2-27), 1.34–1.20 (m, 7 H, including Me-5′′), 1.17 (d, J = 6.0 Hz, 3 H, Me-5′), 1.10 (q, J = 11.6 Hz, 1 H, H_{ax}-18), 0.95–0.85 (m, 6 H, Me-12 and Me-27), 0.92 (s, 9 H, Me_3CSi), 0.81 (d, J = 6.8 Hz, 3 H, Me-24), 0.78 (d, J = 5.2 Hz, 3 H, Me-26), 0.13 (s, 6 H, Me_2Si) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 174.0 (C-1), 142.7 (C-8), 139.5 (C-11), 137.7 (C-4), 133.7 (C-14), 127.0 (C-10), 124.8 (C-15), 119.6 (C-9), 117.1 (C-3), 99.0 (C-1′′), 97.2 (C-21), 93.2 (C-1′), 86.0 (C-13), 82.7 (C-6), 81.6 (C-4′), 79.4 (C-3′), 78.4 (C-3′′), 78.0 (C-7), 77.3 (C-25), 76.1 (C-4′′), 69.0 (C-5), 68.3 (C-5′′ and C-8a), 67.7 (C-17), 66.8 (C-5′), 64.8 (C-19), 56.4, 56.3 (2 OMe), 52.2 (COO*Me*), 46.6 (C-2), 45.0 (C-20), 40.5 (C-18), 38.4 (C-12), 35.8 (C-22), 35.4 (C-26), 34.7 (C-2′′), 34.5 (C-2′), 34.1 (C-16), 31.3 (C-24), 28.1 (C-23), 27.5 (C-27), 25.8 (*Me*$_3$CSi), 19.8 (Me-4), 18.2 (Me$_3$*C*Si), 18.1 (Me-12), 17.6 (Me-5′′), 17.3 (Me-5′), 16.3 (Me-24), 12.4 (Me-26), 11.4 (Me-14 and Me-27), –5.0, –4.6 (Me_2Si) ppm. HRMS (ESI, MeOH): *m*/*z* calcd. for $C_{55}H_{92}O_{15}NaSi$ [M + Na]$^+$ 1043.61032; found 1043.6103.

General Procedure for the Selective Ozonolysis of Secoesters: A catalytic amount of Sudan Red 7B (Aldrich) was added to a magnetically stirred solution of starting material in a 3:1 dichloromethane/ethanol mixture. The solution was cooled to –78 °C under nitrogen and then ozone was bubbled through it. The reaction course was monitored by TLC until complete consumption of the starting material (TLC monitoring was done after a rapid nitrogen purge, independently of the solution colour fading). At the end of the reaction, the solution was purged with nitrogen before addition of the reducing agent.

Sodium Borohydride Reduction: A suspension of solid sodium borohydride (5.0 equiv.) in methanol was added to the reaction mixture at –78 °C and the reaction was monitored by TLC until complete consumption of the intermediates at –78° or 0 °C. The stirred solution was then diluted with water at 0 °C and aqueous 1.0 N HCl was added dropwise down to pH 4. The phases were separated and the aqueous layer was extracted with chloroform (2×). The combined organic extracts were washed with brine (2×), dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

Methyl Sulfide Reduction: The reaction mixture was allowed to warm to room temperature and methyl sulfide (5.0 equiv.) was added whilst stirring. After completion of the reaction (15–20 h, TLC monitoring), the solution was concentrated under reduced pressure and maintained under vacuum until complete evaporation of the methyl sulfide (well-ventilated hood).

In all cases, the crude products were purified by chromatography on silica gel (hexane/AcOEt or dichloromethane/AcOEt mixtures) to give the corresponding IVM subunits.

Ozonolysis of 5-*O*-(*tert*-Butyldimethylsilyl) Ivermectin Ethyl Secoester (Et-5) Followed by $NaBH_4$ Reduction: Ethyl secoester **Et-5** (1.51 g, 1.46 mmol) in 45.0 mL of dichloromethane/ethanol mixture was ozonized according to the general procedure. The solution was purged with nitrogen, and then $NaBH_4$ (276 mg, 7.30 mmol, 5.0 equiv.) in 11.2 mL of methanol was added. The reaction mixture was allowed to warm to 0 °C, maintained at this temperature for 25 min, then extracted as described above and purified by chromatography on silica gel (dichloromethane/AcOEt mixtures, from 100:0 to 0:100) to give, in order of elution, 305 mg (53%) of the 5-*O*-(*tert*-butyldimethylsilyl) HHBF alcohol **11** as a colourless oil and 732 mg (75%) of northern alcohol **7** as a white powder. The spirodiol **10** was found to be present in some intermediate column fractions (TLC) and was purified from another preparative experiment.

5-*O*-(*tert*-Butyldimethylsilyl) Alcohol (11): $[\alpha]_D$ = –46.4 (c = 0.78, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65 (dddd, J = 2.4, 6.3 Hz, 1 H, H-9), 5.41 (app dt, J = 1.4, 2.7 Hz, 1 H, H-3), 4.70 (br. s, 1 H, HO-7), 4.60 (app dt, J = 1.2, 2.4 Hz, 2 H, H_2-8a), 4.49 (m, 1 H, H-5), 4.22 (m, 2 H, COO*C*H_2CH$_3$), 4.13 (ddd, J = 1.2, 6.3 Hz, 2 H, H_2-10), 3.89 (d, J = 4.8 Hz, 1 H, H-6), 3.41 (sext, J = 2.7 Hz, 1 H, H-2), 1.81 (app dt, J = 1.4, 2.7 Hz, 3 H, Me-4), 1.30 (t, J = 7.2 Hz, 3 H, COOCH$_2$*CH*$_3$), 0.92 (s, 9 H, Me_3CSi), 0.13 (s, 6 H, Me_2Si) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 173.7 (C-1), 145.7 (C-8), 137.8 (C-4), 119.1 (C-9), 117.6 (C-3), 82.7 (C-6), 78.3 (C-7), 69.3 (C-5), 68.1 (C-8a), 61.5 (COO*C*H_2CH$_3$), 60.1 (C-10), 46.6 (C-2), 25.8 (*Me*$_3$CSi), 19.9 (Me-4), 18.3 (Me$_3$*C*Si), 14.1 (COOCH$_2$*CH*$_3$), –4.9, –4.6 (Me_2Si) ppm. HRMS (EI): *m*/*z* calcd. for $C_{20}H_{34}O_6Si$ [M$^+$] 398.21247; found 398.2139.

Spirodiol 10: $[\alpha]_D$ = +75.9 (c = 0.82, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3320, 3000–2850, 1459, 1380, 1150–1000, 989 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12 (m, 1 H, H-19), 3.90–3.75 (m, 3 H, H_2-15 and H-17), 3.15 (br. d, J = 9.2 Hz, 1 H, H-25), 2.82 (br. s, 1 H, HO-15), 2.00 (br. dd, J = 4.4, 12.4 Hz, 1 H, H_{eq}-20), 1.91 (br. d, J = 12.4 Hz, 1 H, H_{eq}-18), 1.86–1.20 (m, 12 H, H_2-16, H_{ax}-18, H_{ax}-20, H_2-22, H_2-23, H-24, H-26, H_2-27), 1.61 (s, 1 H, OH-19), 0.92 (t, J = 7.2 Hz, 3 H, Me-27), 0.82 (d, J = 7.2 Hz, 3 H, Me-24), 0.80 (d, J = 6.8 Hz, 3 H, Me-26) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 97.6 (C-21), 77.0 (C-25), 68.9 (C-17), 64.4 (C-19), 61.6 (C-15), 45.0 (C-20), 40.9 (C-18), 37.5 (C-16), 35.5 (C-22 and C-26), 31.1 (C-24), 28.3 (C-23), 27.5 (C-27), 17.4 (Me-24), 12.4 (Me-26), 11.5 (Me-27) ppm. ES MS: *m*/*z* (%) = 309 (100) [M$^+$ + Na], 251 (5), 241 (4).

Northern Alcohol 7: $[\alpha]_D$ = –67.1 (c = 0.85, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3464, 3000–2850, 1458, 1382, 1150–1000, 986 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 (br. t, J = 6.8 Hz, 1 H, H-15), 5.37 (d, J = 3.6 Hz, 1 H, H-1′′), 4.81 (d, J = 3.6 Hz, 1 H, H-1′), 4.10 (m, 1 H, H-19), 3.79 (d, J = 9.6 Hz, 1 H, H-13), 3.78–3.40 (m, 7 H, H_2-11, H-17, H-3′, H-5′, H-3′′ and H-5′′), 3.42 (s, 3 H, OMe), 3.34 (s, 3 H, OMe), 3.21 (t, J = 8.8 Hz, 1 H, H-4′ or H-4′′), 3.16 (t, J = 9.2 Hz, 1 H, H-4′′ or H-4′), 3.11 (dd, J = 1.5, 9.3 Hz, 1 H, H-25), 2.70 (br. s, 1 H, HO-11), 2.58 (br. s, 1 H, HO-4′′), 2.32–2.22 (m, 3 H, H_2-16 and H_{eq}-2′′), 2.13 (ddd, J = 1.0, 4.8, 13.2 Hz, 1 H, H_{eq}-2′), 2.00–1.88 (m, 3 H, including H_{eq}-18 and H_{eq}-20), 1.70 (br. s 1 H, HO-19), 1.64 (br. d, J = 10.0 Hz, 1 H), 1.56 (br. s, 3 H, Me-14), 1.54–1.45 (m, 6 H, H_2-22, H_2-23, H_2-27), 1.35–1.20 (m, 3 H), 1.27 (br. d, 6 H, Me-5′ and Me-5′′), 1.14 (q, J = 11.6 Hz, 1 H, H_{ax}-18), 0.94 (d, J = 12.0 Hz, 1 H), 0.89 (t, J = 7.6 Hz, 3 H, Me-27), 0.80 (d, J = 7.2 Hz, 3 H, Me-12), 0.80 (d, J = 6.8 Hz, 3 H, Me-24), 0.78 (d, J = 6.4 Hz, 3 H, Me-26) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 132.8 (C-14), 128.1 (C-15), 98.4 (C-1′′), 97.2 (C-21), 92.7 (C-1′), 86.3 (C-13), 80.2 (C-4′), 79.5 (C-3′), 78.1 (C-3′′), 77.3 (C-25), 76.0 (C-4′′), 68.1 (C-5′′), 67.6 (C-17), 67.2 (C-5′ and C-11), 64.8 (C-19), 56.4 (2 OMe), 45.0 (C-20), 40.6 (C-18), 37.0 (C-12), 35.8 (C-22), 35.4 (C-26), 34.5 (C-2′′), 34.1 (C-2′ and C-16), 31.3 (C-24), 28.1 (C-23), 27.5 (C-27), 18.6 (Me-24), 17.6 (Me-5′′), 17.4 (Me-5′), 14.2 (Me-12), 12.5 (Me-26), 11.4 (Me-27), 10.9 (Me-14) ppm. ES MS: *m*/*z* (%) = 696 (72) [M$^+$ + Na], 695 (100), 339 (4), 327 (4), 239 (6) ppm. HRMS (EI) *m*/*z* calcd. for $C_{36}H_{64}O_{11}$ [M$^+$] 672.44487; found 672.4442.

Ozonolysis of 5-*O*-(*tert*-Butyldimethylsilyl) Ivermectin Ethyl Secoester (Et-5) Followed by Methyl Sulfide Reduction: Et-5 (1.50 g, 1.45 mmol) in 32.0 mL of dichloromethane/ethanol mixture was ozonized according to the general procedure. The solution was allowed to warm to room temperature, and then methyl sulfide (0.53 mL, 7.23 mmol, 5.0 equiv.) was added. The solution was concentrated and the crude product purified by chromatography on silica gel (hexane/AcOEt mixtures, from 100:0 to 20:80) to give 327 mg (56.9%) of the 5-*O*-(*tert*-butyldimethylsilyl) HHBF aldehyde **12** as a colourless oil and 751 mg (77.3%) of northern aldehyde **9** as a white powder.

Southern Aldehyde 12: IR (KBr): $\tilde{\nu}$ = 3422, 3000–2850, 2774, 2743, 1715, 1255, 1200–1000, 865, 837, 779 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (d, J = 4.5 Hz, 1 H, H-10), 6.23 (app dt, J = 2.5, 4.5 Hz, 1 H, H-9), 5.41 (app dt, J = 1.4, 2.5 Hz, 1 H, H-3), 5.01 (dd, J = 2.5, 17.6 Hz, 1 H, H_A-8a), 4.93 (dd, J = 2.5, 17.6 Hz, 1 H, H_B-8a), 4.49 (m, 1 H, H-5), 4.23 (m, 2 H, COO*CH*$_2$CH$_3$), 3.91 (d, J = 4.8 Hz, 1 H, H-6), 3.40 (sext, J = 2.5 Hz, 1 H, H-2), 1.83 (app dt, J = 1.4, 2.5 Hz, 3 H, Me-4), 1.30 (t, J = 7.2 Hz, 3 H, COOCH$_2$*CH*$_3$), 0.92 (s, 9 H, SiCMe$_3$), 0.14 (s, 6 H, SiMe$_2$) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 190.1 (C-10), 173.3 (C-1), 166.9 (C-8), 137.7 (C-4), 118.2 (C-9), 117.0 (C-3), 81.3 (C-7), 79.3 (C-6), 69.7 (C-8a), 68.7 (C-5), 61.9 (COO*CH*$_2$CH$_3$), 45.2 (C-2), 25.7 (*Me*$_3$CSi), 19.9 (Me-4), 18.3 (Me$_3$*C*Si), 14.0 (COOCH$_2$*CH*$_3$), –5.0, –4.7 (Me$_2$Si) ppm. HRMS (EI) m/z calcd. for $C_{20}H_{32}O_6Si$ [M$^+$] 396.19682; found 396.1971.

Northern Aldehyde 9: $[a]_D$ = –64.1 (c = 0.78, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3450, 3000–2850, 2831, 1730, 1456, 1383, 1150–1000, 985 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.75 (d, J = 3.2 Hz, 1 H, H-11), 5.61 (br. t, J = 6.8 Hz, 1 H, H-15), 5.36 (d, J = 3.2 Hz, 1 H, H-1′′), 4.79 (d, J = 3.2 Hz, 1 H, H-1′), 4.10 (m, 1 H, H-19), 4.09 (d, J = 10.0 Hz, 1 H, H-13), 3.80–3.40 (m, 5 H, H-17, H-3′, H-5′, H-3′′ and H-5′′), 3.44 (s, 3 H, OMe), 3.33 (s, 3 H, OMe), 3.22–3.05 (m, 3 H, H-4′, H-4′′ and H-25), 2.62 (m, 1 H, H-12), 2.51 (br. s, 1 H, HO-4′′), 2.35–2.20 (m, 3 H, H_2-16 and H_{eq}-2′′), 2.11 (dd, J = 4.8, 13.2 Hz, 1 H, H_{eq}-2′), 2.00–1.88 (m, 2 H, H_{eq}-18 and H_{eq}-20), 1.66 (br. s, 1 H, HO-19), 1.64 (br. d, J = 9.5 Hz, 1 H), 1.57 (s, 3 H, Me-14), 1.52–1.46 (m, 6 H, H_2-22, H_2-23 and H_2-27), 1.35–1.18 (m, 4 H), 1.27 (d, J = 6.0 Hz, 3 H, Me-5′), 1.24 (d, J = 6.4 Hz, 3 H, Me-5′′), 1.14 (q, J = 11.6 Hz, 1 H, H_{ax}-18), 0.93 (d, J = 7.2 Hz, 3 H, Me-12), 0.89 (t, J = 7.6 Hz, 3 H, Me-27), 0.80 (d, J = 6.8 Hz, 3 H, Me-24), 0.78 (d, J = 5.2 Hz, 3 H, Me-26) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 204.2 (C-11), 131.4 (C-14), 129.4 (C-15), 98.4 (C-1′′), 97.3 (C-21), 92.8 (C-1′), 82.0 (C-13), 80.2 (C-4′), 79.2 (C-3′), 78.1 (C-3′′), 77.4 (C-25), 76.1 (C-4′′), 68.1 (C-5′′), 67.5 (C-17), 67.2 (C-5′), 64.8 (C-19), 56.4 (2 OMe), 48.0 (C-12), 45.1 (C-20), 40.7 (C-18), 35.8 (C-22), 35.4 (C-26), 34.6 (C-2′′), 34.2 (C-2′ and C-16), 31.3 (C-24), 28.1 (C-23), 27.5 (C-27), 18.5 (Me-24), 17.6 (Me-5′′), 17.4 (Me-5′), 12.5 (Me-26), 11.4 (Me-27), 11.2 (Me-12), 10.7 (Me-14) ppm.

Ozonolysis of 4′′,5-Bis-*O*-(*tert*-butyldimethylsilyl) Ivermectin Ethyl Secoester (Et-6) Followed by $NaBH_4$ Reduction: Bis-silylated Ivermectin ethyl secoester **6** (1.00 g, 0.87 mmol) in 30.0 mL of dichloromethane/ethanol mixture was ozonized according to the general procedure. The solution was purged with nitrogen, and then $NaBH_4$ (165 mg, 4.36 mmol, 5.0 equiv.) in 7.5 mL of methanol was added. The reaction mixture was allowed to warm to 0 °C and maintained at this temperature for 16 min. The solution was extracted as described above to give, after purification by chromatography on silica gel (hexane/AcOEt mixtures, from 90:10 to 50:50), 422 mg (62%) of the silylated northern alcohol **8** as a white solid, and 128 mg (37%) of silylated alcohol **11** as a colourless oil. Data obtained for the latter southern subunit were in full agreement with those described above.

4′′-*O*-(*tert*-Butyldimethylsilyl) Northern Alcohol 8: $[a]_D$ = –64.5 (c = 1.17, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3489, 3000–2850, 1462, 1386, 1256, 1150–1000, 986, 837, 778 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 (br. t, J = 6.8 Hz, 1 H, H-15), 5.28 (d, J = 3.2 Hz, 1 H, H-1′′), 4.80 (d, J = 3.2 Hz, 1 H, H-1′), 4.09 (m, 1 H, H-19), 3.79 (d, J = 9.6 Hz, 1 H, H-13), 3.74–3.30 (m, 7 H, H_2-11, H-17, H-3′, H-5′, H-3′′ and H-5′′), 3.35 (s, 3 H, OMe), 3.33 (s, 3 H, OMe), 3.18 (t, J = 9.9 Hz, 1 H, H-4′), 3.15–3.08 (m, 2 H, H-4′′ and H-25), 2.67 (br. s, 1 H, HO-11), 2.35–2.25 (m, 3 H, H_2-16 and H_{eq}-2′′), 2.12 (ddd, J = 1.0, 4.7, 13.2 Hz, 1 H, H_{eq}-2′), 2.00–1.88 (m, 3 H, including H_{eq}-18, H_{eq}-20), 1.66 (br. s, 1 H, HO-19), 1.64 (br. d, J = 10.2 Hz, 1 H), 1.56 (br. s, 3 H, Me-14), 1.55–1.42 (m, 6 H, H_2-22, H_2-23, H_2-27), 1.35–1.20 (m, 4 H), 1.27 (d, J = 6.4 Hz, 3 H, Me-5′), 1.21 (d, J = 6.4 Hz, 3 H, Me-5′′), 1.13 (q, J = 11.8 Hz, 1 H, H_{ax}-18), 0.90 (s, 9 H, Me$_3$CSi), 0.89 (app t, J = 7.6 Hz, 3 H, Me-27), 0.80 (d, J = 6.8 Hz, 3 H, Me-24), 0.80 (d, J = 7.2 Hz, 3 H, Me-12), 0.78 (d, J = 6.0 Hz, 3 H, Me-26), 0.10, 0.08 (s, 6 H, Me$_2$Si) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 132.9 (C-14), 128.0 (C-15), 98.6 (C-1′′), 97.2 (C-21), 92.7 (C-1′), 86.3 (C-13), 80.8 (C-4′), 79.4 (C-3′), 78.4 (C-3′′), 77.3 (C-4′′), 77.0 (C-25), 69.0 (C-5′′), 67.6 (C-17), 67.3 (C-11 or C-5′), 67.2 (C-5′ or C-11), 64.8 (C-19), 56.5, 56.3 (2 OMe), 45.1 (C-20), 40.6 (C-18), 37.0 (C-12), 35.8 (C-22), 35.4 (C-26), 34.6 (C-2′ and C-2′′), 34.1 (C-16), 31.3 (C-24), 28.1 (C-23), 27.5 (C-27), 26.0 (*Me*$_3$CSi), 18.6 (Me-24), 18.2 (Me-5′′ and Me$_3$*C*Si), 17.4 (Me-5′), 14.2 (Me-12), 12.5 (Me-26), 11.4 (Me-27), 10.9 (Me-14), –4.8, –4.0 (Me$_2$Si) ppm. ES MS: m/z (%) = 810 (100) [M$^+$ + Na], 641 (16), 447 (10), 441 (16), 399 (11), 227 (42).

Reduction of 5-*O*-(*tert*-Butyldimethylsilyl) Ivermectin Ethyl Secoester (Et-5): $NaBH_4$ (275 mg, 7.27 mmol, 25.0 equiv.) in 1.5 mL of methanol was added to a solution of **Et-5** (304 mg, 0.29 mmol) in 6 mL of a 3:1 mixture of dichloromethane and ethanol at 0 °C. The stirred solution was allowed to warm to room temperature and the reaction mixture was maintained at this temperature for 20 h. Then, the solution was diluted with water (10 mL) and 0.5 N aqueous HCl was added dropwise down to pH 4. The phases were separated and the aqueous layer extracted with diethyl ether (2×20 mL). The combined organic extracts was washed with brine (2×20 mL), dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give, after purification by flash chromatography on silica gel (hexane/AcOEt mixtures, from 70:30 to 20:80), 90 mg (30.8%) of the expected Ivermectin secoalcohol as a white powder. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 143.9 (C-8), 139.1 (C-11), 136.5 (C-4), 133.6 (C-14), 127.1 (C-10), 124.8 (C-15), 122.0 (C-9), 118.6 (C-3), 99.3 (C-1′′), 97.2 (C-21), 93.2 (C-1′), 85.8 (C-13), 82.6 (C-6), 81.2 (C-4′), 79.1 (C-3′), 77.3 (C-3′′ and C-25), 75.9 (C-4′′), 69.3 (C-5), 68.1 (C-5′′ and C-8a), 67.7 (C-17), 66.8 (C-5′), 64.9 (C-19), 61.9 (C-1), 56.4, 56.0 (2 OMe), 45.0 (C-20), 40.5 (C-18), 38.6 (C-12), 35.8 (C-22), 35.4 (C-26), 34.7 (C-2′′), 34.4 (C-2′), 34.1 (C-16), 31.3 (C-24), 29.6 (C-2), 28.1 (C-23), 27.5 (C-27), 25.8 (*Me*$_3$CSi), 19.9 (Me-4), 18.3 (Me-12 and Me$_3$*C*Si), 17.6 (Me-5′′), 17.3 (Me-5′), 16.6 (Me-24), 12.4 (Me-26), 11.4 (Me-27), 11.3 (Me-14), –4.9, –4.6 (Me$_2$Si) ppm.

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