Formal Convergent Synthesis of Ivermectin Aglycone – A Synthetic Approach to the C10–C25 Subunit of Avermectins 2b

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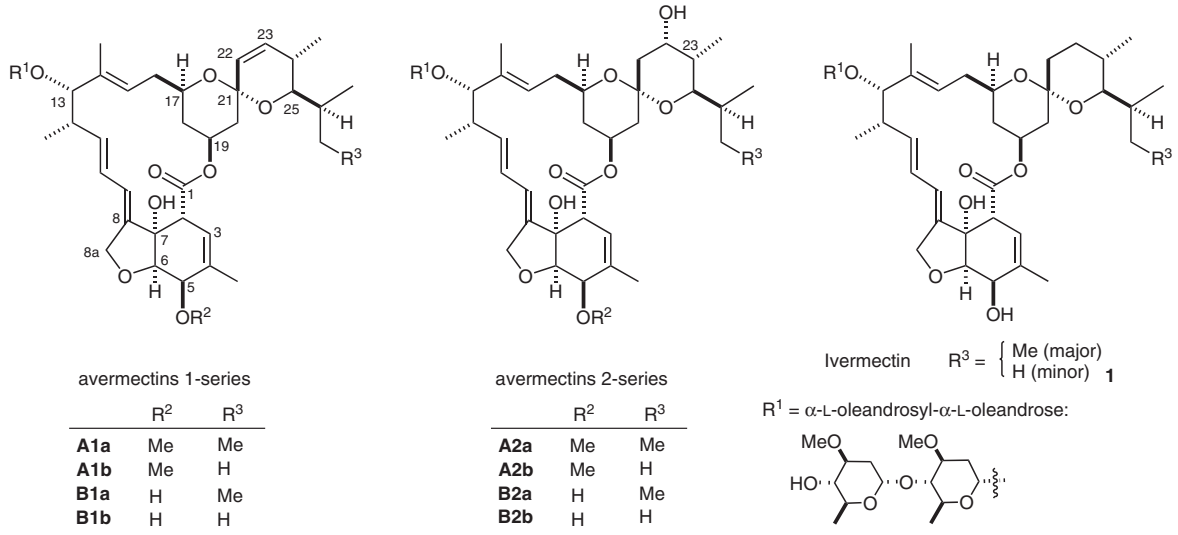
Abstract: A convergent, two-fragment synthesis of the C10–C25 northern moiety of avermectins has been developed. Along with our previous work in this area, the present contribution represents a formal synthesis of Ivermectin aglycone. Furthermore, according to a strategy leading to non γ-pyranone adducts from the condensation reaction between acetylacetone dianion and convenient aldehydes, 23-hydroxylated C10–C25 northern building blocks required for the synthesis of the avermectins series 2b were prepared. Subsequent unexpected kinetically favored unnatural (21*S*)-spiro isomers were obtained under mild cyclization conditions.

Key words: antibiotics, stereoselective synthesis, macrocycles, spiro compounds, cyclizations

The avermectins, isolated from *Streptomyces avermitilis* in the late 1970s, constitute a group of closely related 16-membered macrocyclic lactones of high biological and economical importance.[1] To date, eight natural avermectins have been isolated as fermentation products from *Streptomyces avermitilis* (Figure 1). Only subtle structural differences exist between them. A safer and more potent mixture of semi-synthetic avermectin B1a and B1b, hydrogenated at the level of the C22–C23 double bond, was developed in the 1980s by Merck under the name Ivermectin (IVM; **1**).[2]

Their unique broad-spectrum antihelminthic activity both on endo and ecto-parasite infections made avermectins, for more than 25 years, the most important class of pesticides and veterinary drugs for livestock and companion animals. Moreover, this class of microfilaricidal compounds also found application in human medicine, initially for human onchocerciasis, and more recently against other filariases. With the aim of developing new orally effective drugs against leishmaniasis, we recently successfully prepared semi-synthetic analogues of **1** exhibiting promising antileishmanial activity.[3] Huge synthetic efforts towards avermectins have culminated in several total syntheses of different members of this class at the end of the last century.[4] For our own part, we have described a total synthesis of the aglycone of **1** according to a two-subunit convergent strategy involving a C10–C11 disconnection.[5]

Despite its high potency, several drawbacks progressively appeared along with the intensive use of avermectin antibiotics, such as environmental soil, river and marine pol-



	R^2	R^3
A1a	Me	Me
A1b	Me	H
B1a	H	Me
B1b	H	H

	R^2	R^3
A2a	Me	Me
A2b	Me	H
B2a	H	Me
B2b	H	H

R^3 = { Me (major) / H (minor) } **1**

Figure 1 Eight natural avermectins and Ivermectin

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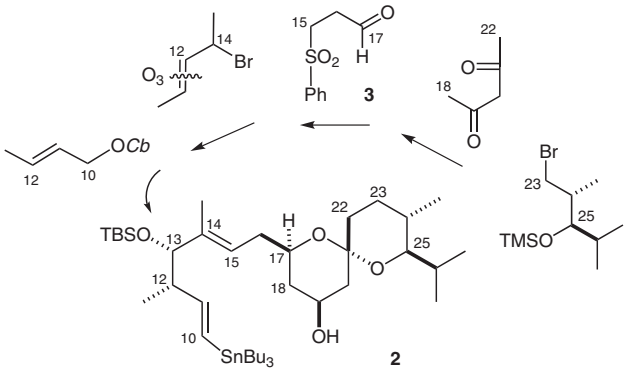
lution, or collateral toxicity effects, for example towards soil invertebrates.[6] Antihelmintic resistance also appears to be a major concern in the case of animal nematode treatment,[7] even though this is not yet the case for human filariases.[8] Continuing efforts towards developing new molecules exhibiting higher potencies with an optimized activity spectrum and improved safety profiles led to several new semi-synthetic avermectin analogues, particularly with regards to their optimized insecticidal and acaricidal properties.[9]

Furthermore, promising biological activities of avermectins have also been recently reported in the field of antitumor therapy. Based on the known inhibiting effect of avermectins on P-glycoprotein, one key factor involved in multidrug-resistance of tumors,[10] Korustov's group in Russia demonstrated the beneficial effect of some avermectin members when added to other antitumor drugs in the treatment of multidrug-resistant cell tumors.[11]

Taken together, the scientific interest in the avermectin class of antibiotics is in full renaissance in several aspects. In a continuation of our program on avermectins, we present here our results on the synthesis of avermectins of the 2b-series for which little effort has so far been devoted. To our knowledge, the only synthesis of the northern sub-unit of avermectin A2b, bearing the desired axial 23-OH, was reported by the group of E. J. Thomas: the key step for installing this functional group involves a C22–C23 epoxide ring-opening reaction by a dithiane anion at C-21.[12] The avermectin 2b series was chosen as key targets since they could potentially lead to all the other avermectins through a dehydration reaction.

Two main goals were pursued during the present study. We first wanted to develop a three-fragment disconnection allowing access to the C10–C25 northern subunit in a more convergent manner than the previous linear approach developed in the case of the C10–C25 stannane **2** used for the synthesis of IVM aglycone (Scheme 1).[5]

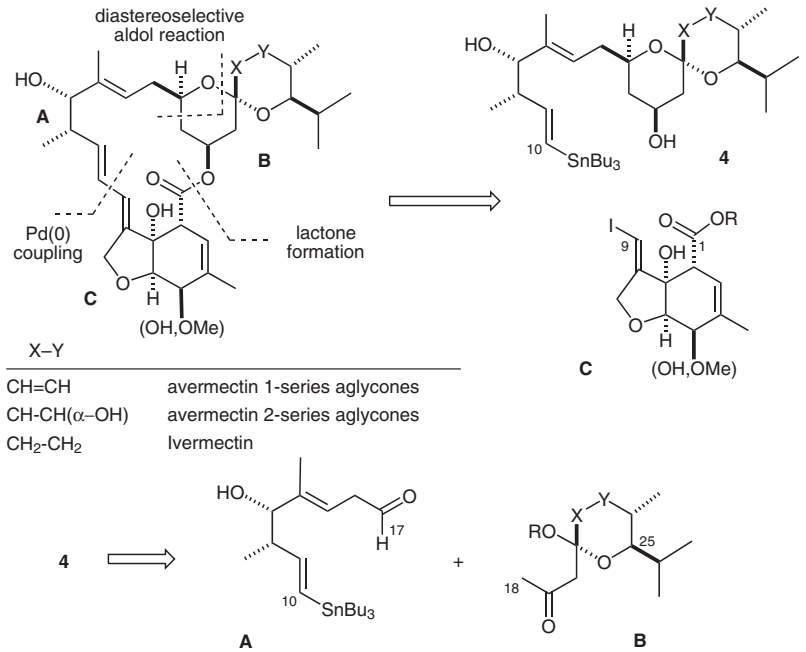


Scheme 1 Linear approach to the C10–C25 subunit of IVM **1**

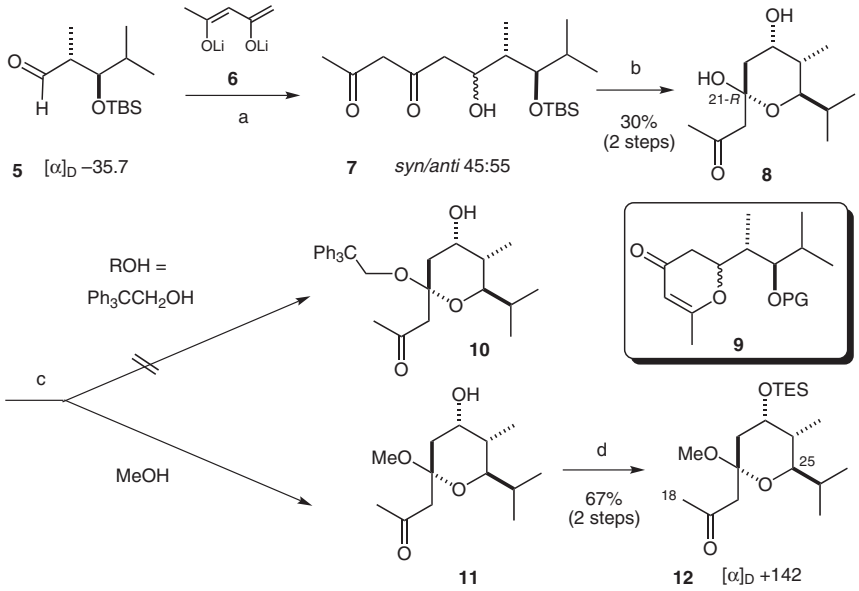
In order to develop a more convergent and practical approach to the C10–C25 portion of avermectins, it was decided to take advantage of the key diastereocontrolled aldol reaction occurring at the level of the condensation of sulfonyl aldehyde **3** with the enolate of the bulky keto acetal intermediate of type **B** (see **21**, X–Y = CH_2–CH_2), where R = triphenylethyl (see Scheme 2).[13] An interesting 3:1 diastereoselectivity in favor of the expected chirality at C-17 was obtained, a bias tentatively explained by unhindered *Re*-face attack of the lithium enolate.[5]

Therefore, a three-fragment convergent approach was envisioned as shown in Scheme 2, where a stereocontrolled aldol reaction similar to that already described above was expected to couple subunits of type **A** and **B**.

For the remaining steps of the total synthesis, which involves a subsequent cross-coupling reaction between the northern C10–C25 (*E*)-vinylstannane **4** and the corre-



Scheme 2 Three-fragment **A**–**B**–**C** disconnection for avermectins



Scheme 3 *Reagents and conditions*: (a) LDA (2 equiv), –78 °C, THF; (b) (i) TBAF, DMF, 60 °C, 1 h; (ii) Chromatography; (c) Mont. K10, $MeNO_3$, ROH, 5 min, r.t.; (d) TESCl, imidazole, DMF.

sponding southern vinyl iodide counterpart **C** followed by the final macrolactonization step, it was decided to exploit the route previously developed for **1**.[14]

A second key strategic point was to apply our published anti-Danishefsky spiroketal methodology, which allows the construction of acetonyl tetrahydropyran subunits of type **B**,[15] instead of the usually expected γ-pyranone of type **9** (see Scheme 3).[16]

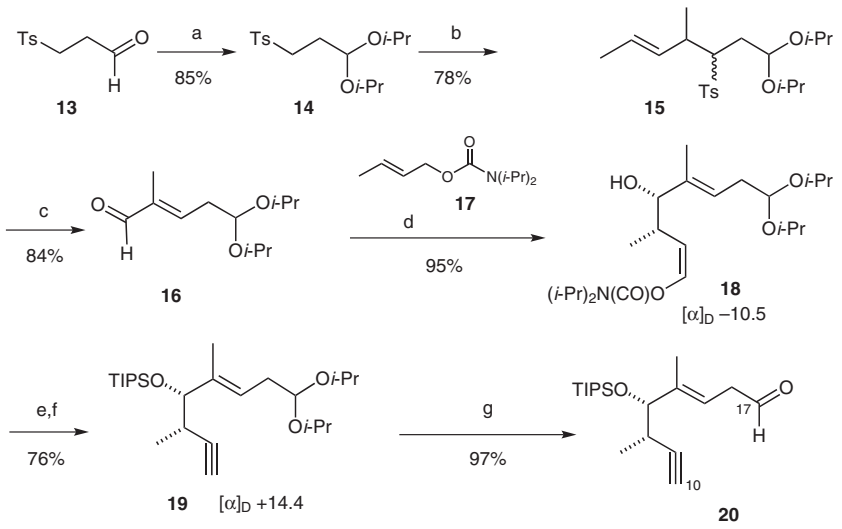
The C18–C25 subunit was synthesized according to the previously described strategy.[14] Although the presence of a bulky protecting group, such as a triisopropylsilyl group, at the secondary hydroxy of **5** has been shown to favor formation of the expected *anti*,*anti*-diastereomer, for practical reasons, the less favorable *tert*-butyldimethylsilyl (TBS) group was selected. Therefore, the known, enantiopure TBS-*O*-protected (2*S*,3*R*)-*anti*-aldehyde **5** was chosen as a starting material, which represents the unique source of asymmetry for the spiroketal unit.[17] Condensation of **5** with the 2,4-pentanedione dianion **6** cleanly afforded the crude aldolization adduct as a 45:55 mixture of diastereomers, which was immediately treated with an excess of tetrabutylammonium fluoride (TBAF) in *N*,*N*-dimethylformamide (DMF) at 60 °C to give, after purification, the required hemiketal **8** in 30% yield from **5**. No trace of the γ-pyranone **9** was detected. At this level, we expected to be able to use a bulky ketal protecting group to direct the subsequent aldol condensation with the C11–C17 aldehyde. Unfortunately, all attempts to prepare a voluminous ketal such as **10** failed. Strong stabilizing hydrogen bonds between the two axial hydroxy groups at C-21 and C-23 as well as with the carbonyl group at C-19, could favor thermodynamically-controlled retro-condensation of the bulky 2,2,2-triphenylethanol. Therefore, hemiketal **8** was subsequently transformed under our previously described mild conditions into the protected methylketal **11**. Protection of the secondary hydroxy by a triethylsilyl group, afforded **12**, which was ready to be condensed with the C10–C17 subunit.

The preparation of the C10–C17 aldehyde, depicted in Scheme 4, turned out to be straightforward. Attention only had to be paid to the choice of the aldehyde protecting group at C-17, as some difficulties were encountered at the deprotection step. Forcing acidic conditions invariably resulted in the production of the undesired C15–C17 conjugated aldehyde. The choice of the isopropyl acetal protecting group, thanks to the mild conditions required for its removal, solved this problem.[18]

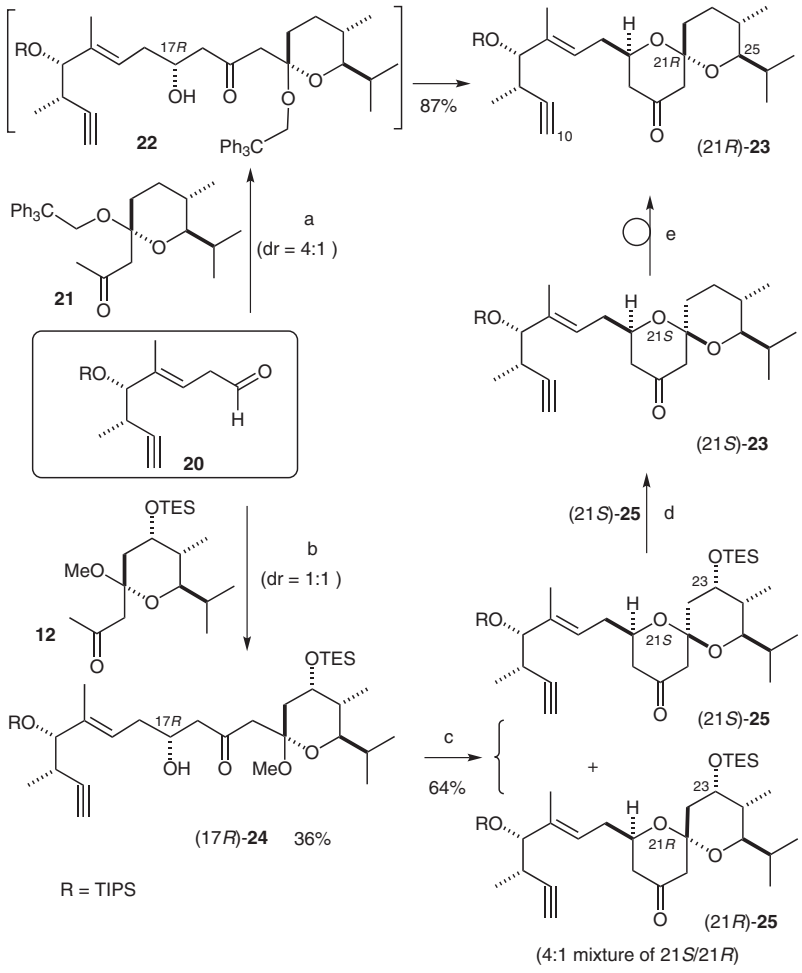
The sulfonyl diisopropyl acetal **14**, derived from the known 3-tosylpropanal **13**, was condensed with 2-bromopent-3-ene to give a mixture of diastereomers that was treated directly with ozone to yield, after triethylamine treatment, the conjugated (*E*)-aldehyde **15** according to an Isobe sequence similar to that already successfully applied by us during the synthesis of **1**.[19] A Hoppe enantioselective homoaldol reaction in the presence of (–)-spartein[20] between **16** and the (*E*)-butenyl-*N*,*N*-diisopropylcarbamate **17**, furnished the *anti*-homoaldol **18** in excellent yield. ^{1}H NMR analysis of the (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl ester of **18** (Mosher ester)[21] revealed a 93:7 enantiomeric ratio.

Protection of the secondary hydroxy group using triisopropylsilyl triflate followed by treatment with an excess of *s*-BuLi gave the acetylenic derivative **19** in 76% yield. Mild deprotection of the isopropyl acetal group delivered the C10–C17 aldehyde **20**, which was ready to be coupled with the preceding C18–C25 subunit.

In a preliminary approach to the final stage of the synthesis of the C10–C25 subunit of Avermectin series 2b, the viability of the novel C10–C17 + C18–C25 strategy was tested using acetal **21**, possessing the bulky 2,2,2-triphe-



Scheme 4 *Reagents and conditions*: (a) *i*-PrOH, CH_2Cl_2, CSA, 3Å Sieves; (b) *n*-BuLi, THF, HMPA then 2-bromopent-3-ene; (c) O_3, CH_2Cl_2, Py (1%) then Et_3N; (d) *s*-BuLi, (–)-spartein, $Ti(OiPr)_4$; (e) TIPSOTf, CH_2Cl_2, 2,6-Lutidine; (f) *s*-BuLi (3.8 equiv), Et_2O, –78 °C; (g) aq PTSA (0.1 M), THF, 60 °C, 45 min.



Scheme 5 *Reagents and conditions*: (a) (i) LDA (1.1 equiv), –78 °C→r.t.; (ii) aq HCl work-up; (b) (i) LDA (1.1 equiv), –78 °C→r.t.; (ii) chromatography; (c) PPTS, MeOH, r.t.; (d) (i) HF/Py; (ii) thiocarbonyldiimidazole, THF, reflux, 24 h; (iii) Bu_3SnH, AIBN, toluene, reflux; (e) HCl, $CHCl_3$, r.t.

nylethyl ketal protecting group previously developed for the synthesis of the IVM **1** (Scheme 5). Besides providing more convergent access to the C10–C25 subunit of this standard macrolide, this synthesis would provide a reference molecule that could be used to correlate the 23-hydroxylated C10–C25 subunits of avermectins 2b.

Condensation of the lithium enolate of **21** with aldehyde **20** afforded the crude aldol **22** as a 4:1 mixture of diastereomers (Scheme 5). Subsequent acidic workup led to the expected spiroketal subunit (21*R*)-**23** as the major diastereomer, the spectroscopic and physicochemical data of which agreed completely with the analogous northern spiroketal sub-units previously synthesized.[5] Interestingly, this new convergent route represents a marked improvement for the synthesis of this Ivermectin subunit.

Turning to the 23-hydroxylated series, the lithium enolate of methyl ketal **12** was condensed with aldehyde **20** to afford a 1:1 mixture of C17-diastereomers that were separated by column chromatography to give pure (17*R*)-**24**. The latter aldol adduct was smoothly converted into a 4:1 mixture of spiroketals **25** under mild Lewis acid conditions.

In order to ascertain the stereochemistry at C-17 and at the spirocenter C-21, the separated major cyclic epimer (21*S*)-**25** was subsequently submitted to a Barton–McCombie deoxygenation reaction. To our surprise, the deoxygenated spiroketal obtained through HF/Py mediated selective desilylation at C-23, followed by Bu_3SnH/AIBN treatment of the corresponding thioimidazolide, was found to differ from (21*R*)-**23** previously obtained from **21**. The milder conditions used to cyclise (17*R*)-**24** compared with **22** (in order to avoid possible undesirable formation of γ-pyranone type adducts **9**), were claimed to be responsible for the major formation of the kinetically controlled (21*S*)-**25**, spiroketal which was then deoxygenated into the 'unnatural' spiroketal (21*S*)-**23** as depicted in Scheme 5. Treatment of the latter with HCl/$CHCl_3$ resulted in its total transformation into a product which was shown to be completely identical to the thermodynamically more stable 'natural' spiroketal (21*R*)-**23** that exhibits a double reciprocal anomeric effect. Therefore the minor isomer (21*R*)-**25** was deduced to be the 'natural' northern moiety required for the synthesis of avermectins 2b.

The convergent **A**–**B** two-fragment synthesis of the known northern precursor (21*R*)-**23** of Ivermectin **1** using the bulky ketal **21** represents a marked improvement to the already published linear route. Thus, the present study represents a formal synthesis of Ivermectin aglycone **1**.

Dealing with the synthesis of the avermectins 2b series from ketal **12**, further transformation of the C10–C25 subunit **25** into the genuine northern sub-unit of type **4** (cf. Scheme 2) requires either successfully attempted or fully described steps on similar substrates to those used in the IVM **1** precedent: spiro-equilibration at C-21, stereoselective reduction at C-19 and hydrostannylation of the triple bond. Subsequent Stille cross-coupling reaction of **4** with our previously described southern vinyl iodide **C**, followed by a macrolactonization reaction would afford the final macrolide. The present study demonstrates the viability of the synthesis of the whole family of avermectin macrolides using a convergent approach to the fully functionalized spiroketal moiety of these molecules.

Mass spectra were obtained on a Nermag R10-10B spectrometer via either direct introduction by chemical ionization with ammonia (CI, NH_3) or electron impact (EI). Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Cameca 250 or on a Bruker AM 400 instrument using $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS) or referenced to residual $CHCl_3$ (7.27 ppm). ^{13}C NMR spectra were recorded on a Bruker AM 400 instrument at 100.57 MHz, the chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). When necessary, assignments were obtained using *J*-modulation experiments. Infrared (IR) spectra were obtained on a Perkin–Elmer 599 model instrument (wavelength are given in cm^{-1}). Optical rotations were determined on a Perkin-Elmer 241 instrument. Microanalyses were performed by the analytical laboratory of the University of Pierre and Marie Curie, Paris. Solvent distillation methods: THF and Et_2O from sodium-benzophenone; CH_2Cl_2 and $CHCl_3$ from CaH_2; Et_3N, DMF and pyridine from CaH_2; pentane, hexane and petroleum ether from phosphoric anhydride; toluene from sodium-benzophenone. Thin Layer Chromatography (TLC) was performed on pre-coated plates of silica gel 60 F254 (Merck, Art. 7735). Flash chromatography was performed on silica gel Merck 60, 70–230 mesh (Art. 7736) or Merck 60, 230–400 mesh (Art. 9385). Medium pressure liquid chromatography (MPLC) was carried out on Lobar column Merck Lichroprep R Si 60 (Art. 10401) or with Büchi MPLC column filled with silica gel Merck 60, 230–400 mesh (Art. 9385) or Merck Lichroprep R Si 60 (Art. 139050 or 9336). Basic silica refers to $NaHCO_3$-treated silica gel Merck Art.7734. Preparation of a stock solution of LDA: To a solution of diisopropylamine (58 mL, 415 mmol) in anhydrous THF (65 mL, 800 mmol) at –70 °C, was added dropwise, *n*-BuLi (250 mL, 1.6 M in hexanes, 400 mmol). The mixture was warmed to 0 °C for 30 min to give a solution of LDA (1.1 M), which was stored at 0 °C. IUPAC nomenclature was used for all compounds. For the description of ^{1}H NMR and ^{13}C NMR spectra, avermectin numbering is used.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyl)oxy-2,4-dimethylpentanal (5)

A solution containing pure (2*S*,3*R*)-3-(*tert*-butyldimethylsilyl)oxy-2,4-dimethylpentan-1-ol (5 g, 20.3 mmol), DMSO (40 mL) and Et_3N (20 mL, 142 mmol, 7 equiv), was vigorously stirred at r.t. while pyridine-SO_3 complex (11 g, 71 mmol, 3.5 equiv) was added portion-wise over 30 min. The reaction mixture was stirred for 30 min at r.t. and cooled to 0–5 °C (ice–water bath) before addition of a mixture of 50% aq AcOH (100 mL) and crushed ice (100 g). Extraction with pentane according to usual conditions (washings with H_2O) afforded a residue, which was diluted in pentane (5 mL) and filtrated over a silica pad (elution with 50 mL Et_2O). The solvent was removed under reduced pressure to give pure aldehyde **5**.

Yield: 4.6 g (93%); $[\alpha]_D^{20}$ –35.7 (*c* 0.1, CH_2Cl_2) {Lit. $[\alpha]_D$ –35.6 (*c* 0.1, CH_2Cl_2)}.

IR (film): 2980, 2940, 2900, 2840, 1730, 1470, 1390, 1260 cm^{-1}.

^{1}H NMR (250 MHz): δ = 0.90, 0.93 [2 × d, *J* = 6.9 Hz, 6 H, $(CH_3)_2$C-26], 1.11 (d, *J* = 7.1 Hz, 3 H, CH_3C-24), 1.85 (m, 1 H, H-26), 2.54 (m, 1 H, H-24), 3.68 (dd, *J* = 4.8, 4.2 Hz, 1 H, H-25), 9.8 (d, *J* = 2.5 Hz, 1 H, CHO).

^{13}C NMR: δ = –4.3, –4.1 [$(CH_3)_2$Si], 11.9, 18.2, 18.7 [*C*H_3C-24 and (CH_3)$_2$C-26], 25.6 [$(CH_3)_3$*C*-Si], 25.9 [(CH_3)$_3$C-Si], 32.8 (C-26), 49.8 (C-24), 79.1 (C-25), 205.0 (CHO).

All data are in agreement with reported values.[15,17b]

(2*R*,4*S*,5*S*,6*R*)-2-Acetonyl-2,4-dihydroxy-6-isopropyl-5-methyltetrahydropyran (8)

(a) *Aldol reaction*: A solution of LDA (1.1 M in THF, 36.0 mL, 39.5 mmol, 2.1 equiv) was cooled to 0–5 °C (ice–water bath) under nitrogen, and 2,4-pentanedione (2.0 mL, 19.7 mmol, 1.05 equiv) was added dropwise to the yellow solution. After 30 min at 0 °C, the reaction mixture was cooled to –78 °C (dry ice–acetone bath) and a solution of aldehyde **5** (4.6 g, 18.8 mmol) in THF (10 mL) was added slowly. The resulting mixture was stirred for another 30 min, then hydrolyzed with sat. aq NH_4Cl. Usual work-up with Et_2O (successive washings with H_2O and brine) followed by silica flash chromatography (Et_2O–PE, 0:1→1:1) afforded pure **7** as a mixture of the two *anti*/*syn* diastereomeric adducts in a 45:55 ratio (6.33 g, 97% yield). This crude mixture was directly submitted to the subsequent cyclization step.

(b) *Desilylation–cyclization of aldol mixture 7*: To a solution of the preceding mixture (6.33 g, 18.4 mmol) in DMF (180 mL) was added in one portion, TBAF trihydrate (36 g, 0.13 mol, 6 equiv). The resulting solution was heated to 50 °C for 1 h, then allowed to cool to r.t. and EtOAc and H_2O were successively added. After decanting and separation, the aqueous layer was extracted with EtOAc (2×). The combined organic phases were treated as usual (washings with brine) to give a crude dark-brown residue (7.62 g), which was diluted with EtOAc and filtered over a silica pad (25 g silica; EtOAc–pentane, 4:1) to afford a mixture of diastereomers, which was subsequently separated by Lobar MPLC silica chromatography (EtOAc–PE, 1:40→4:1) to give, in order of elution: the required lactol **8** and its (21*S*)-epimeric congener.

(2*R*,4*S*,5*S*,6*R*)-2-Acetonyl-2,4-dihydroxy-6-isopropyl-5-methyltetrahydropyran (8)

Yield: 1.32 g (30% over two steps); white solid; mp 66–67 °C (Et_2O–pentane); $[\alpha]_D^{20}$ +68 (*c* 1.0, $CHCl_3$).

All spectroscopic data were in full agreement with the same product already described in the racemic series.[15]

(2*R*,4*R*,5*S*,6*R*)-2-Acetonyl-2,4-dihydroxy-6-isopropyl-5-methyltetrahydropyran

Yield: 1.22 g (28%); white solid; mp 86–87 °C (Et_2O–pentane); $[\alpha]_D^{20}$ +6 (*c* 2.6, $CHCl_3$).

All spectroscopic data were also in full agreement with the same product already described in the racemic series.[15]

(2*R*,4*S*,5*S*,6*R*)-2-Acetonyl-6-isopropyl-2-methoxy-5-methyl-4-(triethylsilyl)oxytetrahydropyran (12)

To a solution of hemiketal **8** (1.8 g, 15.2 mmol) in a mixture of MeOH (29 mL) and $MeNO_2$ (49 mL), was added in one portion at r.t., Montmorillonite K-10 (18 g). After 5 min, the reaction mixture was quickly filtered through a pad composed of (from the top to the bottom): sand, silica, K_2CO_3 and $MgSO_4$ layers, each of which being of approximately equal thickness (eluent: EtOAc). The filtrate was concentrated under reduced pressure (temperature of the heating bath should not exceed 30 °C) to give crude methyl ketal **11** (1.77 g, 87% yield) that was directly protected as a *O*-TES ether. Spectroscopic data for this intermediate were in full agreement with the same product already described in the racemic series.[15]

To a solution of the preceding methyl ketal **11** (1.77 g, 7.25 mmol) in DMF (30 mL) was added at r.t., imidazole (2.5 g, 36.2 mmol, 5 equiv). The resulting solution was cooled to –35 °C and TESCl (2.73 g, 3.0 mL, 18.1 mmol, 2.5 equiv) was added dropwise. After 10 min, the reaction mixture was allowed to warm to 0 °C then, after 10 min, added to dilute aq Na_2CO_3 (100 mL). Usual work-up with Et_2O (washings with H_2O and brine) followed by flash chromatography on $NaHCO_3$-treated silica (EtOAc–PE, 0:100→15:85), afforded the pure 23-O-silylated compound **12**.

Yield: 1.88 g (67% for the 2 steps); $[\alpha]_D^{20}$ +142 (*c* 2.7, $CHCl_3$).

IR (film): 2960, 2900, 2880, 1720, 1460, 1350, 1100, 1010 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.58 [q, *J* = 7.6 Hz, 6 H, (CH_3CH_2)$_3$Si], 0.81 (d, *J* = 6.6 Hz, 3 H, CH_3C-24), 0.83 (d, *J* = 7.0 Hz, 3 H, CH_3C-26), 0.96 [t, *J* = 7.6 Hz, 9 H, (CH_3CH_2)$_3$Si], 1.07 (d, *J* = 7 Hz, 3 H, CH_3C-26), 1.50 (dqd, *J* = 10.0, 7.0, 5.0 Hz, 1 H, H-24), 1.82 (sept d, *J* = 6.6, 2.4 Hz, 1 H, H-26), 1.84 (m, 2 H, H_2-22), 2.24 (s, 3 H, CH_3-18), 2.37, 2.95 (2 × d, *J* = 12.1 Hz, 2 H, H_2-20), 3.21 (s, 3 H, CH_3O), 3.62 (dd, *J* = 10.0, 2.4 Hz, 1 H, H-25), 3.85 (ddd, *J* = 5.0, 3.3, 3.1 Hz, 1 H, H-23). Peaks were assigned with the aid of H,H-COSY and HETCOR experiments.

^{13}C NMR (100.57 MHz): δ = 4.9 [(CH_3CH_2)$_3$Si], 6.8 [CH_3CH_2)$_3$Si], 13.6 (*C*H_3C-24), 14.3, 20.3 [(*C*H_3)$_2$C-26], 28.4 (C-26), 32.0 (C-18), 36.3 (C-24), 39.4 (C-22), 47.3 (CH_3O), 50.4 (C-20), 68.9 (C-23), 73.0 (C-25), 98.2 (C-21), 207.4 (C-19).

MS (CI, NH_3): *m*/*z* = 344 (MH^+ + NH_3 – MeOH), 327, 195, 153, 132, 120.

Anal. Calcd. for $C_{19}H_{38}O_4Si$: C, 63.64; H, 10.68. Found: C, 63.74; H, 10.57.

1-(3,3-Diisopropoxypropane-1-sulfonyl)-4-methylbenzene (14)

Aldehyde **13** was synthesized according to the procedure of Cooper and Dolby.[22] To a solution of TsNa (98 g, 0.55 mol) in a mixture of H_2O (550 mL) and THF (275 mL), was added dropwise, at 0 °C, AcOH (32 mL, 0.55 mol) over 1 h, then acrolein (33 mL, 0.5 mol) in THF (138 mL). The reaction mixture was stirred for 24 h before addition of H_2O (1 L). Usual work-up with CH_2Cl_2 including washing with sat. aq $NaHCO_3$ and brine, gave 3-(*p*-toluenesulfonyl)propanal **13**, which was sufficiently pure to be used in the next step without purification.

Yield: 87.4 g (82%); colorless oil.

IR (film): 1725, 1600, 1500, 1450, 1400, 1300, 1175 cm^{-1}.

^{1}H NMR (400 MHz): δ = 2.44 (s, 3 H, CH_3Ar), 2.92 (t, *J* = 7.5 Hz, 2 H, H_2-2), 3.40 (t, *J* = 7.5 Hz, 2 H, H_2-3), 7.42, 7.80 (2 × d, *J* = 8.2 Hz, 2 × 2 H, 4 × Ar-H), 9.70 (s, 1 H, CHO).

^{13}C NMR: δ = 21.6 (*C*H_3Ar), 36.6 (*C*H_2CHO), 49.1 (CH_2SO_2), 128.0, 130.0 (2 × 2Ar-*C*H), 135.6 (CH_3*C*-Ar), 145.1 (SO_2*C*-Ar), 197.1 (CHO).

MS (CI, NH_3): *m*/*z* = 213 [MH^+], 124.

Anal. Calcd. for $C_{10}H_{12}O_3S$: C, 56.59; H, 5.70. Found: C, 56.74; H, 5.82.

Aldehyde **13** (42 g, 0.2 mol) was added to a mixture containing *i*-PrOH (100 mL, 1.3 mol), CH_2Cl_2 (200 mL) and CSA (1.5 g). The reaction mixture was stirred under reflux for 3 h, then freshly activated 3Å molecular sieves were added and the mixture was stirred at r.t. for 15 h. After addition of sat. aq $NaHCO_3$, the mixture was stirred another 2 h and filtered over a pad of Celite and decanted. The aqueous phase was extracted with Et_2O containing 1% Et_3N, and the combined organic phases were treated as usual to afford a crude product that was subsequently purified on a preparative Lobar MPLC column coated with silica Merck Lichroprep Si 60 (Art. 13905; Et_2O–PE, 15:85→50:50) to give pure sulfonyl acetal **14**.

Yield: 53.4 g (85%); white solid.

^{1}H NMR (400 MHz): δ = 1.13 (2 × d, *J* = 6.1 Hz, 12 H, 4 × CH_3CH), 1.96 (m, 2 H, CH_2CH), 2.46 (s, 3 H, CH_3Ar), 3.19 (m, 2 H, CH_2SO_2), 3.79 [hept, *J* = 6.2 Hz, 2 H, 2 × C*H*(CH_3)$_2$], 4.67 [t,

J = 4.9 Hz, 1 H, C*H*(O*i*Pr)$_2$], 7.36, 7.79 (2 × d, J = 8.2 Hz, 2 × 2 H, 4 × Ar-H).

^{13}C NMR: δ = 21.4 (*C*H$_3$-Ar), 22.2, 23.0 (2 × *C*H$_3$CH), 28.8 (*C*H$_2$CH$_2$SO$_2$), 51.6 (CH$_2$SO$_2$), 68.4 (2 × OC*H*CH$_3$), 97.6 (*C*H-*i*Pr), 127.8, 129.7 (2 × 2*C*H-Ar), 136.1 (CH$_3$*C*-Ar), 144.4 (SO$_2$*C*-Ar).

MS (CI, NH$_3$): m/z = 332 [MH$^+$ + 17], 315 [MH$^+$], 255.

Anal. Calcd. for $C_{16}H_{26}O_4S$: C, 61.12; H, 8.33; Found: C, 61.03; H, 8.53.

1-(1,1-Diisopropoxy-4-methylhept-5-en-3-sulfonyl)-4-methylbenzene (15)

To a solution of sulfone **14** (32 g, 0.1 mol) in THF (350 mL), was slowly added (30 min) at –78 °C under N_2, *n*-BuLi (1.57 M in hexanes, 70 mL, 1.1 mol, 1.1 equiv). After being stirred for 30 min at –78 °C, HMPA (18 mL) was carefully added, followed by freshly prepared 4-bromopent-2-ene[23] (17.9 g, 0.12 mol, 1.2 equiv). After 2 h at –78 °C, the reaction mixture was allowed to warm to 0 °C before being quenched with sat aq NaHCO$_3$. After addition of Et$_3$N (2 mL), usual work-up with Et$_2$O afforded the crude material, which was subsequently submitted to preparative silica MPLC chromatography as above (Et$_2$O–PE, 0:1→1:1) to give pure **15**.

Yield: 30.4 g (78% yield); pale-yellow oil; 1:1 mixture of diastereomers.

^{1}H NMR (400 MHz): δ (1:1 mixture of diastereomers) = 1.0–1.2 (m, 15 H, 5 × C*H*$_3$CH), 1.62 [t, J = 5.6 Hz, 3 H, C*H*$_3$CH=], 1.83, 2.10 (2 × m, 2 H, CH$_2$), 2.46 (s, 3 H, C*H*$_3$Ar), 2.76 (m, 1 H, C*H*CH=), 3.08, 3.19 (2 × m, 1 H, CHSO$_2$), 3.75 [m, 2 H, 2 × C*H*(CH$_3$)$_2$], 4.65 [m, J = 4.9 Hz, 1 H, C*H*(O*i*Pr)$_2$], 5.32–5.48 (m, 2 H, 2 × CH=), 7.36, 7.77 (2 × d, J = 8.2 Hz, 2 × 2 H, 4 × Ar-H).

^{13}C NMR: δ (1:1 mixture of diastereomers) = 14.3, 17.8, 18.0, 18.8, 21.5, 22.0, 22.1, 22.8, 22.9, 23.3 and 23.3 (*C*H$_3$), 30.3 and 31.2 (*C*H$_2$CHSO$_2$), 35.0 (*C*HCH=), 64.4 and 65.6 (CHSO$_2$), 68.6, 68.8, 68.9 and 68.9 [2 × O*C*H(CH$_3$)$_2$], 98.6 and 98.6 [*C*H(O*i*Pr)$_2$], 125.3 and 126.5 (CH*C*H=), 128.5, 128.8, 129.6 and 129.7 (4 × Ar-*C*H), 130.4 and 133.2 (CH$_3$*C*H=), 135.9 and 136.1 (CH$_3$*C*-Ar), 144.3 (SO$_2$*C*-Ar).

MS (CI, NH$_3$): m/z = 400 [MH$^+$ + 17], 323, 167, 109.

Anal. Calcd. for $C_{21}H_{34}O_4S$: C, 65.93; H, 8.96. Found: C, 66.00; H, 9.05.

(*E*)-5,5-Diisopropoxy-2-methylpent-2-enal (16)

Ozone enriched oxygen was gently bubbled at –78 °C through a solution containing sulfone **18** (6.0 g, 16 mmol) in CH$_2$Cl$_2$ (160 mL) containing 1% v/v of pyridine (1.6 mL) until a blue coloration persisted. While still at –78 °C, the excess of ozone was flushed with a nitrogen stream for 30 min. The temperature was then allowed to warm to r.t. and Et$_3$N (2.3 mL) added. After stirring overnight, the orange-red reaction mixture was carefully evaporated in vacuo with a rotavapor, behind a safety shield (**CAUTION**). The remaining oily residue was diluted with pentane and partially purified on a flash chromatography column (Et$_2$O–PE, 0:100→70:30) to afford impure material which was subsequently submitted to a MPLC purification step (CH$_2$Cl$_2$–PE, 40:60 with a Et$_2$O gradient from 100:0→70:30) to furnished the expected pure (*E*)-aldehyde **16**. This aldehyde was immediately used for the subsequent homoaldol condensation.

Yield: 2.82 g (84%); colorless oil.

IR (film): 2970, 2920, 1685, 1640, 1030 cm^{-1}.

^{1}H NMR (400 MHz): δ = 1.20 (m, 12 H, 4 × C*H*$_3$CH), 1.78 (d, J = 1.0 Hz, 3 H, CH$_3$C-14), 2.66 (t, J = 6.1 Hz, 2 H, H$_2$-16), 3.89 [hept., J = 5.5 Hz, 2 H, 2 × OC*H*(CH$_3$)$_2$], 4.73 [t, J = 5.2 Hz, 1 H, C*H*(O*i*Pr)$_2$], 6.58 (dq, J = 7.2, 1.0 Hz, 1 H, H-15), 9.44 (s, 1 H, CHO).

^{13}C NMR: δ = 10.1 (*C*H$_3$C-14), 22.4 and 23.2 (4 × *C*H$_3$CH), 35.6 (C-16), 68.4 [2 × OC*H*(CH$_3$)$_2$], 98.6 [*C*H(O*i*Pr)$_2$], 140.1 (C-15), 149.1 (C-14), 195.1 (CHO).

MS (CI, NH$_3$): m/z = 232 [MH$^+$ + 17], 155.

(–)-Vinyl-*N*,*N*-diisopropylcarbamate (18)

To a well stirred solution containing freshly distilled (–)-spartein (5.94 g, 25.6 mmol, 1.1 equiv) in a mixture of pentane (81 mL) and cyclohexane (11.6 mL), was successively added via cannula at –78 °C, *s*-BuLi (1.3 M in cyclohexane–hexanes, 19.6 mL, 25.6 mmol) and the crotylcarbamate **17** (4.87 g, 24.5 mmol, 1.05 equiv) in pentane (24.5 mL). After stirring 45 min at –90 °C, during which time a white thick precipitate was formed, a pre-cooled solution of titanium isopropoxide (30.5 mL, 102 mmol, 4 equiv/spartein) was added dropwise via syringe. The reaction mixture became deep-red and, after stirring a further 15 min, aldehyde **16** (4.98 g, 23.3 mmol) in pentane (5 mL) was added via cannula at –90 °C. The reaction mixture was stirred for 30 min at –78 °C, then at r.t. for 30 min before addition of ice-cold sat. aq NH$_4$Cl (500 mL) and Et$_2$O (500 mL). This slurry was filtrated on Celite (washings with Et$_2$O) and the filtrate decanted. Re-extraction of the aqueous phase and work-up as usual gave the crude *anti*-homoaldol product **18**. ^{1}H NMR analysis revealed this product to be sufficiently pure for the next step.

Yield: 9.10 g (95%); $[\alpha]_D^{20}$ –10.5 (*c* 2.07, CHCl$_3$).

IR (film): 3460, 2970, 1705, 770 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.88 (d, J = 6.8 Hz, 3 H, C*H*$_3$CH-12), 1.14–1.23 [m, 24 H, 4 × (C*H*$_3$)$_2$CH], 1.65 (s, 1 H, CH$_3$C-14), 2.38 (t, J = 6.25 Hz, 2 H, H$_2$-16), 2.90 (m, 1 H, H-12), 3.67 (d, J = 9.1 Hz, 1 H, H-13), 3.88 [m, 2 H, 2 × OC*H*(CH$_3$)$_2$], 3.90, 4.26 {2 × br m, 2 H, [(CH$_3$)$_2$C*H*]$_2$N}, 4.55 (t, J = 8 Hz, 1 H, H-17), 4.65 (dd, J = 9.9, 6.3 Hz, 1 H, H-11), 5.44 (t, J = 6.8 Hz, 1 H, H-15), 7.19 (d, J = 6.3 Hz, 1 H, H-10).

^{13}C NMR: δ = 11.0 (*C*H$_3$C-14), 17.4 (*C*H$_3$C-12), 20.3 and 21.5 {br, 6 H, 2 × N[CH(*C*H$_3$)$_2$]}, 22.5, 22.6, 23.3 and 23.4 [2 × OCH(*C*H$_3$)$_2$], 34.2 (C-16), 34.5 (C-12), 45.7 and 46.9 {br, 2 × N[*C*H(CH$_3$)$_2$]}, 67.7 and 67.8 [2 × O*C*H(CH$_3$)$_2$], 82.0 (C-13), 99.8 (C-17), 113.3 (C-11), 124.1 (C-15), 136.6 (C-14), 137.0 (C-10), 152.8 (C=O).

MS (CI, NH$_3$): m/z = 414 [MH$^+$ + 17], 336, 128.

MTPA-ester of **18** (Steglich procedure):[24] To a solution of DCC (50 mg, 0.24 mmol) and DMAP (2.4 mg, 0.014 mmol, 0.1 equiv) were added, under nitrogen at r.t., crude **18** (80 mg diluted with 0.5 mL CH$_2$Cl$_2$), then (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(*R*)-(+)-MTPA; 56.7 mg, 0.24 mmol, 1.25 equiv). The reaction mixture was stirred overnight, then pentane (2 mL) was added and the mixture filtered. The filtrate was added to H$_2$O and extracted with CH$_2$Cl$_2$–pentane (1:1, 2×). Washings with sat. aq NaHCO$_3$, then H$_2$O, followed by drying with MgSO$_4$ and evaporation, delivered the crude product that was directly analyzed by ^{1}H NMR.

(5*E*,3*S*,4*S*)-8,8-Diisopropoxy-3,5-dimethyl-4-[(triisopropylsilyl)oxy]-oct-5-en-1-yne (19)

To a solution of **21** (207 mg, 0.5 mmol) in CH$_2$Cl$_2$ (2 mL) was added at 0 °C, 2,6-lutidine (0.14 mL, 1.2 mmol, 2.6 equiv), then dropwise, triisopropylsilyl trifluoromethanesulfonate (0.17 mL, 0.65 mmol, 1.3 equiv). The reaction mixture was stirred for 10 min at 0 °C, then quenched with H$_2$O. Usual work-up including extraction with Et$_2$O, followed by MPLC silica column purification (Et$_2$O–PE, 0:100→70:30) afforded the pure *O*-triisopropylsilyl-protected carbamate.

Yield: 250 mg (91%); pale-yellow oil.

^{1}H NMR (400 MHz): δ = 0.99–1.17 [m, 48 H, 7 × (C*H*$_3$)$_2$CH, 3 × CHSi and CH$_3$C-12], 1.70 (s, 1 H, CH$_3$C-14), 2.48 (t, J = 6.1 Hz, 2 H, H$_2$-16), 3.16 (m, 1 H, H-12), 3.64 and 3.93 {2 × br m, 2 H, 2 ×

N[C*H*(CH_3)$_2$]}, 3.79 [sext, *J* = 6.1 Hz, 2 H, 2 × OC*H*(CH_3)$_2$], 4.07 (d, *J* = 7.4 Hz, 1 H, H-13), 4.61 (t, *J* = 5.4 Hz, 1 H, H-17), 4.73 (dd, *J* = 9.9, 6.6 Hz, 1 H, H-11), 5.59 (t, *J* = 6.6 Hz, 1 H, H-15), 6.55 (d, *J* = 7.6 Hz, 1 H, H-10).

^{13}C NMR: δ = 12.1 (*C*H_3C-14), 12.4 and 12.6 [3 × Si*C*H(CH_3)$_2$], 17.6 (*C*H_3C-12), 17.7, 18.2 and 18.2 [6 × Si(CH*C*H_3], 20.5 and 21.5 {br, 2 × N[CH(*C*H_3)$_2$]}, 22.4, 22.6, 23.3 and 23.4 [2 × OCH(*C*H_3)$_2$], 34.2 (C-16), 35.7 (C-12), 45.7 and 46.8 {br, 2 × N[*C*H(CH_3)$_2$]}, 67.5 and 67.6 [2 × OC*H*(CH_3)$_2$], 82.6 (C-13), 99.8 (C-17), 114.4 (C-11), 122.7 (C-15), 134.8 (C-10), 138.1 (C-14), 153.0 (C=O).

MS (CI, NH_3): *m*/*z* = 587 [MH^+ + 17], 336.

A solution of *s*-BuLi (1.28 M in cyclohexane/hexanes, 0.8 mL, 1 mmol, 3.8 equiv) was slowly added at –78 °C to a solution of the above intermediate (150 mg, 0.26 mmol) in Et_2O (2 mL). After 15 min at –78 °C, the temperature was allowed to reach 0 °C for 15 min, then the reaction mixture was quenched with sat. aq NH_4Cl and extracted as usual with Et_2O. The crude product was purified on silica gel MPLC column coated with Lichroprep silica Merck Art. 9336 (hexane–Et_2O, 100:0→85:15) to give the pure acetylenic derivative **19**.

Yield: 102 mg (83%); $[\alpha]_D^{20}$ +14.4 (*c* 2.0, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 0.95–1.20 [m, 36 H, 5 (CH_3)$_2$CH, 3 × CHSi and CH_3C-12], 1.61 (s, 1 H, CH_3C-14), 1.86 (d, *J* = 2.4 Hz, 1 H, H-10), 2.43 (t, *J* = 6.15 Hz, 2 H, H_2-16), 2.67 (qd, *J* = 7.5 and 2.4 Hz, 1 H, H-12), 3.76 [m, 2 H, 2 × OC*H*(CH_3)$_2$], 4.24 (d, *J* = 7.7 Hz, 1 H, H-13), 4.56 (t, *J* = 5.4 Hz, 1 H, H-17), 5.61 (t, *J* = 7.1 Hz, 1 H, H-15).

^{13}C NMR: δ = 11.9 (*C*H_3C-14), 12.6 [3 × Si*C*H(CH_3)$_2$], 17.2 (*C*H_3C-12), 18.2 and 18.2 [6 × Si(CH*C*H_3], 22.4, 22.6, 23.4 and 23.4 [2 × OCH(*C*H_3)$_2$], 32.1 (C-12), 34.1 (C-16), 67.6 and 67.6 [2 × O*C*H(CH_3)$_2$], 69.3 (C-10), 81.7 (C-13), 87.9 (C-11) 99.7 (C-17), 123.6 (C-15), 137.0 (C-14).

MS (CI, NH_3): *m*/*z* = 442 [MH^+ + 17], 191.

(3*E*,5*R*,6*S*)-5-[(Triisopropylsilyl)oxy]-4,6-dimethyl-oct-3-en-7-ynal (20)

To a solution of diisopropylacetal **19** (2.72 g, 6.41 mmol) in THF (50 mL) was added in one portion an aqueous solution of TsOH (0.1 M, 3.2 mL, 0.32 mmol, 0.05 equiv). The resulting solution was heated to 55–60 °C for 45 min and then cooled to 0–5 °C (ice–water bath) before addition of pentane (50 mL) and H_2O (5 mL). After decanting and separation, the organic layer was quickly washed with brine (2 × 100 mL) to give, after usual treatment, aldehyde **20**. This compound was fairly unstable; it could not be purified by chromatography without extensive loss of material and was therefore immediately used for the subsequent aldolization step.

Yield: 2 g (97%); oil.

^{1}H NMR (400 MHz): δ = 1.08–1.12 [m, 24 H, 3 × (CH_3)$_2$CH, 3 × CHSi and CH_3C-12], 1.67 (br s, 3 H, CH_3C-14), 2.05 (d, *J* = 2.5 Hz, 1 H, H-10), 2.65 (qd, *J* = 7.2, 2.5 Hz, 1 H, H-12), 3.18 (d, *J* = 6.0 Hz, 2 H, H-16), 4.22 (d, *J* = 6.8 Hz, 1 H, H-13), 5.62 (br t, *J* = 7.2 Hz, 1 H, H-15), 9.66 (t, *J* = 2.0 Hz, 1 H, CHO). No trace of the corresponding α,β-conjugated aldehyde was found.

Condensation of Aldehyde (20) with (2*R*,5*S*,6*R*)-2-Acetonyl-6-isopropyl-5-methyl-4-(triethylsilyl)oxy-2-(2,2,2-triphenylethoxy)tetrahydropyran (21)

To a solution containing the known optically active bulky ketal **21** (47 mg, 0.1 mmol) in THF (12 mL), was added at –78 °C under nitrogen, LDA (1.05 M in THF, 0.105 mL, 1.1 equiv). After 30 min at this temperature, optically active aldehyde **20** (46 mg, 0.14 mmol, 1.4 equiv) in THF (1 mL) was added, via cannula to the resulting anion solution. After a further 30 min, the reaction mixture was quenched with sat. aq NH_4Cl and Et_2O was added. After decanting and re-extraction of the aqueous phase with Et_2O (3×), the combined organic phases were washed with brine, diluted aqueous HCl, then brine again before drying and evaporation under the usual conditions. Silica MPLC purification (Et_2O–hexanes, 0:100→15:85) afforded the expected condensation adduct **23** (44 mg, 87% yield) as a c.a. 4:1 mixture of epimers at C-17. The major isomer was thoroughly identified as [2*R*(2*E*,4*S*,5*S*),6*R*,8*R*,9*S*,10*S*]-2-[3,5-dimethyl-4-(triisopropylsilyl)oxyhept-2-en-6-ynyl]-8-isopropyl-9-methyl-1,7-dioxaspiro[5.5]undecan-4-one [(21*R*)-**23**] by comparison with the northern spiroketal subunit of 22,23-dihydroavermectin B1b **1**, previously synthesized in our group.

^{1}H NMR (400 MHz): δ (4:1 mixture of isomers, only values for the major isomer reported) = 0.81, 0.82, 0.90 [3 × d, *J* = 7.0 Hz, 9 H, CH_3C-24 and (CH_3)$_2$C-26], 1.07 [br m, 24 H, (*i*Pr)$_3$-Si and CH_3C-12], 1.40–1.80 (m, 5 H), 1.69 (s, 3 H, CH_3C-14), 1.85 (sept d, *J* = 7.0, 2.0 Hz, 1 H, H-26), 2.03 (d, *J* = 2.3 Hz, 1 H, H-10), 2.21 (dd, *J* = 14.3, 13.8 Hz, 1 H, Ha-18), 2.36 (m, 5 H), 2.64 (qint d, *J* = 7.0, 2.4 Hz, 1 H, H-12), 3.08 (dd, *J* = 9.7, 2.0 Hz, 1 H, H-25), 3.94 (m, 1 H, H-17), 4.16 (d, *J* = 7.5 Hz, 1 H, H-13), 5.50 (br t, *J* = 7.0 Hz, 1 H, H-15).

MS (CI, NH_3): *m*/*z* = 536 [MH^+ + 17], 519 [MH^+].

Condensation of Aldehyde (20) with (2*R*,4*S*,5*S*,6*R*)-2-Acetonyl-6-isopropyl-2-methoxy-5-methyl-4-(triethylsilyl)oxytetrahydropyran (12)

In a well-dried, round-bottomed flask, under nitrogen at –78 °C, were successively introduced THF (20 mL), a solution of LDA (1.05 M in THF, 5.54 mL, 5.54 mmol, 1.1 equiv) via a syringe and, after 5 min, via cannula, a solution of acetal **12** (1.80 g, 5.04 mmol) in THF (19 mL). After 5 min at 0 °C, the reaction mixture was cooled to –78 °C and stirred for 15 min, then a solution of aldehyde **20** (2 g, 6.21 mmol, 1.2 equiv) in THF (14 mL) was added dropwise via syringe. After 15 min, the reaction mixture was hydrolyzed with sat. aq NH_4Cl (15 mL) then allowed to warm to r.t. and poured into a mixture of Et_2O (100 mL) and sat. aq NH_4Cl (100 mL). The aqueous layer was decanted and re-extracted twice with Et_2O. Usual work-up, including washings with brine, afforded the crude aldol product which was shown to be a 1:1 mixture of diastereomers by ^{1}H NMR analysis. Purification by silica MPLC (Et_2O–PE, 0:1→1:1) gave, in order of elution: the less polar 'natural' diastereomer (17*R*)-**24** (1.23 g, 36%) then the more polar 'unnatural' epimer (17*S*)-**24** (1.26 g, 37%).

[6*E*(2*R*,4*S*,5*S*,6*R*)4*S*,8*S*,9*S*]-7,9-Dimethyl-1-[6-isopropyl-2-methoxy-5-methyl-4-(triethylsilyl)oxytetrahydropyran-2-yl]-4-hydroxy-8-(triisopropylsilyl)oxyundec-6-en-10-yn-2-one [(17*R*)-24]

$[\alpha]_D^{20}$ +63 (*c* 1.2, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 0.58 [q, *J* = 7.5 Hz, 6 H, (CH_3CH_2)$_3$Si], 0.81 (d, *J* = 6.9 Hz, 3 H, CH_3C-24), 0.86 (d, *J* = 6.8 Hz, 3 H, CH_3C-26), 0.97 [t, *J* = 7.5 Hz, 9 H, (CH_3CH$_2$)$_3$-Si], 1.07 [br m, 24 H, (*i*Pr)$_3$-Si, CH_3C-12 and CH_3C-26], 1.52 (m, 1 H, H-24), 1.64 (s, 3 H, CH_3C-14), 1.81 (m, 1 H, H-26), 1.83 (br d, *J* = 4.5 Hz, 2 H, H_2-22), 2.04 (d, *J* = 2.3 Hz, 1 H, H-10), 2.22 (m, 2 H, H_2-16), 2.43 (d, *J* = 12.4 Hz, 1 H, Ha-20), 2.64 (quint d, *J* = 7.0, 2.3 Hz, 1 H, H-12), 2.73 (m, 2 H, H_2-18), 2.91 (d, *J* = 12.4 Hz, 1 H, Hb-20), 2.93 (d, *J* = 6.2 Hz, 1 H, HOC-17), 3.18 (s, 3 H, CH_3-O), 3.62 (dd, *J* = 10, 2.3 Hz, 1 H, H-25), 3.85 (q, *J* = 3.9 Hz, 1 H, H-23), 4.07 (m, 1 H, H-17), 4.15 (d, *J* = 7.0 Hz, 1 H, H-13), 5.43 (br t, *J* = 6.2 Hz, 1 H, H-15).

^{13}C NMR: δ = 4.9 [(CH_3CH_2)$_3$Si], 6.8 [(*C*H_3CH$_2$)$_3$Si], 12.2 (*C*H_3C-14), 12.5 {[(CH_3)$_2$*C*H]$_3$Si}, 13.6 (*C*H_3C-24), 14.4, 16.9, 20.3 [(*C*H_3)$_2$C-26 and *C*H_3C-12], 18.1 {[(*C*H_3)$_2$CH]$_3$Si}, 28.4 (C-26), 32.3 (C-12), 34.6 (C-16), 36.3 (C-24), 39.7 (C-22), 47.4 (CH_3-O), 50.3, 50.5 (C-18 and C-20), 67.3 (C-17), 68.9 (C-23), 69.6 (C-10),

73.2 (d, C-25), 81.0 (C-13), 87.6 (C-11), 98.2 (C-21), 123.5 (C-15), 138.1 (C-14), 209.9 (C-19).

MS (CI, NH_3): *m*/*z* = 666, 649, 517, 410, 327, 239.

[6*E*(2*R*,4*S*,5*S*,6*R*)4*R*,8*S*,9*S*]-7,9-Dimethyl-1-[6-isopropyl-2-methoxy-5-methyl-4-(triethylsilyl)oxytetrahydropyran-2-yl]-4-hydroxy-8-(triisopropylsilyl)oxyundec-6-en-10-yn-2-one [(17*S*)-24]

$[\alpha]_D^{20}$ +93 (*c* 1.7, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 0.58 [q, *J* = 7.5 Hz, 6 H, $(CH_3CH_2)_3Si$], 0.81, 0.82 (d, *J* = 6.8 Hz, 6 H, CH_3C-24 and CH_3C-26), 0.96 [t, *J* = 7.5 Hz, 9 H, $(CH_3CH_2)_3Si$], 1.07 (br m, 27 H, (*i*Pr)$_3$-Si, CH_3C-12 and CH_3C-26), 1.48 (m, 1 H, H-24), 1.62 (s, 3 H, CH_3C-14), 1.84 (sept d, *J* = 6.8, 2.2 Hz, 1 H, H-26), 1.86 (m, 2 H, H_2-22), 2.04 (d, *J* = 2.3 Hz, 1 H, H-10), 2.22 (br t, *J* = 6.2 Hz, 2 H, H_2-16), 2.37 (d, *J* = 12.3 Hz, 1 H, Ha-20), 2.60 (m, 1 H, H-12), 2.62 (dd, *J* = 15.3, 8.8 Hz, 1 H, Ha-18), 2.88 (dd, *J* = 15.3, 2.5 Hz, 1 H, Hb-18), 2.95 (d, *J* = 12.3 Hz, 1 H, Hb-20), 3.06 (d, *J* = 3.0 Hz, 1 H, HOC-17), 3.19 (s, 3 H, CH_3-O), 3.61 (dd, *J* = 10.0, 2.2 Hz, 1 H, H-25), 3.85 (q, *J* = 3.1 Hz, 1 H, H-23), 4.05 (m, 1 H, H-17), 4.13 (d, *J* = 7.1 Hz, 1 H, H-13), 5.46 (br t, *J* = 7.0 Hz, 1 H, H-15).

^{13}C NMR: δ = 4.9 $[(CH_3CH_2)_3Si]$, 6.8 $[(CH_3CH_2)_3Si]$, 12.1 (CH_3C-14), 12.5 $\{[(CH_3)_2CH]_3Si\}$, 13.6, 14.4, 17.0, 20.3 [CH_3C-24, $(CH_3)_2$C-26, CH_3C-12], 18.1 $\{[(CH_3)_2CH]_3Si\}$, 28.4 (C-26), 32.2 (C-12), 34.5 (C-16), 36.3 (C-24), 39.6 (C-22), 47.4 (CH_3-O), 50.1 (C-20), 50.4 (C-18), 67.5 (C-17), 68.9 (C-23), 69.5 (C-10), 73.2 (C-25), 81.1 (C-13), 87.6 (C-11), 98.3 (C-21), 123.4 (C-15), 137.9 (C-14), 209.0 (C-19).

MS (CI, NH_3): *m*/*z* = 666, 649, 517, 327, 301, 285, 169.

Spiroketalisation Reaction of (17*R*)-24

To a solution of (17*R*)-**24** (~0.05 M, 550 mg, 0.81 mmol) in THF, was added, at r.t., pyridinium *p*-toluenesulfonate (PPTS; 2 equiv). The reaction mixture was stirred for 30 min, and then quenched with sat. aq $NaHCO_3$. Extraction with Et_2O according to the usual work-up, including washings with sat. aq $CuSO_4$, afforded the crude spiroketal adducts, which were subsequently separated by silica MPLC chromatography (Et_2O–PE, 0:1→3:7) to give, in order of elution: the major less polar 'unnatural' spiro-epimer (21*S*)-**25** (275 mg, 52% yield) and the minor 'natural' spiro-epimer (21*R*)-**25** (64 mg, 12% yield).

[2*R*(2*E*,4*S*,5*S*),6*S*,8*R*,9*S*,10*S*]-2-[3,5-Dimethyl-4-(triisopropylsilyl)oxy-hept-2-en-6-ynyl]-8-isopropyl-9-methyl-4-(triethylsilyl)oxy-1,7-dioxaspiro[5.5]undecan-4-one [(21*S*)-25]

$[\alpha]_D^{20}$ –13.4 (*c* 1.9, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 0.62 [q, *J* = 7.5 Hz, 6 H, $(CH_3CH_2)_3Si$], 0.80 (d, *J* = 6.9 Hz, 3 H, CH_3C-24), 0.86, 0.88 [2 × d, *J* = 6.7 Hz, 6 H, $(CH_3)_2$C-26], 0.98 [t, *J* = 7.5 Hz, 9 H, $(CH_3CH_2)_3Si$], 1.06 [br m, 24 H, (*i*Pr)$_3$Si and CH_3C-12], 1.60 (m, 1 H, H-24), 1.62 (s, 3 H, CH_3C-14), 1.75 (dd, *J* = 13.8, 3.1 Hz, 1 H, Ha-22), 1.78 (m, 1 H, H-26), 1.90 (dd, *J* = 13.8, 3.3 Hz, 1 H, Hb-22), 2.00 (d, *J* = 2.4 Hz, 1 H, H-10), 2.40, 2.58 (br m, 4 H, H_2-16 and H_2-18), 2.59 (d, *J* = 16.4 Hz, 1 H, Ha-20), 2.60 (m, 1 H, H-12), 3.38 (d, *J* = 16.4 Hz, 1 H, Hb-20), 3.39 (dd, *J* = 10.0, 2.5 Hz, 1 H, H-25), 3.99 (q, *J* = 3.0 Hz, 1 H, H-23), 4.12 (d, *J* = 7.3 Hz, 1 H, H-13), 4.15 (m, 1 H, H-17), 5.46 (br t, *J* = 6.0 Hz, 1 H, H-15).

^{13}C NMR: δ = 4.8 $[(CH_3CH_2)_3Si]$, 7.0 $[(CH_3CH_2)_3Si]$, 12.1 (CH_3C-14), 12.5 $\{[(CH_3)_2CH]_3Si\}$, 13.4 (CH_3C-24), 14.2, 20.4 $[(CH_3)_2$C-26], 17.1 (CH_3C-12), 18.1 $\{[(CH_3)_2CH]_3Si\}$, 28.0 (C-26), 32.0 (C-12), 34.8, 44.1 (C-18 and C-16), 36.2 (C-24), 42.9 (C-22), 47.2 (C-20), 69.4 (C-10), 70.4 (C-23), 71.0 (C-17), 76.5 (C-25), 81.3 (C-13), 87.6 (C-11), 99.6 (C-21), 123.0 (C-15), 137.9 (C-14), 207.2 (C-19).

(21*R*)-25

^{1}H NMR (400 MHz): δ = 0.63 [q, *J* = 7.5 Hz, 6 H, $(CH_3CH_2)_3Si$], 0.79 (d, *J* = 7.0 Hz, 3 H, CH_3C-26), 0.82 (d, *J* = 7.0 Hz, 3 H, CH_3C-24), 0.91 (d, *J* = 7.0 Hz, 3 H, CH_3C-26), 1.00 [t, *J* = 7.5 Hz, 9 H, $(CH_3CH_2)_3Si$], 1.07 [br m, 24 H, (*i*Pr)$_3$Si, CH_3C-12], 1.59 (dd, *J* = 14.0, 4.3 Hz, 1 H, Ha-22), 1.60 (m, 1 H, H-24), 1.63 (s, 3 H, CH_3C-14), 1.76 (sept d, *J* = 7.0, 2.0 Hz, 1 H, H-26), 2.02 (dd, *J* = 14.0, 3.0 Hz, 1 H, Hb-22), 2.03 (d, *J* = 2.3 Hz, 1 H, H-10), 2.16 (dd, *J* = 14.0, 11.0 Hz, 1 H, Ha-18), 2.34 (m, 5 H, H_2-16, Hb-18 and H_2-20), 2.63 (quint d, *J* = 7.1, 2.3 Hz, 1 H, H-12), 3.58 (dd, *J* = 10.0, 2.0 Hz, 1 H, H-25), 3.90 (q, *J* = 3.1 Hz, 1 H, H-23), 3.98 (m, 1 H, H-17), 4.16 (d, *J* = 7.1 Hz, 1 H, H-13), 5.52 (br t, *J* = 7.0 Hz, 1 H, H-15).

^{13}C NMR: δ = 5.0 $[(CH_3CH_2)_3Si]$, 7.0 $[(CH_3CH_2)_3Si]$, 12.1 (CH_3C-14), 12.6 $\{[(CH_3)_2CH]_3Si\}$, 13.5 (CH_3C-24), 13.9, 20.3 $[(CH_3)_2$C-26], 16.9 (CH_3C-12), 18.1 $\{[(CH_3)_2CH]_3Si\}$, 28.3 (C-26), 32.3 (C-12), 32.8, 46.1, 52.3 (C-16, C-18 and C-20), 36.2 (C-24), 42.0 (C-22), 68.3 (C-17), 68.9 (C-23), 69.5 (C-10), 72.5 (C-25), 81.1 (C-13), 87.6 (C-11), 99.1 (C-21), 123.0 (C-15), 137.9 (C-14), 206.3 (C-19).

MS (CI, NH_3): *m*/*z* = 666 [MH^+ + 17], 649 [MH^+], 595, 517, 475, 319, 255, 223.

Spiroketalisation Reaction of (17*S*)-24

For comparison studies, the 'unnatural' (17*S*)-epimer was also submitted to a spiroketalisation reaction using the above conditions. From pure (17*S*)-**24** (630 mg, 0.92 mmol), two epimeric spiroketal adducts were obtained: a major less polar (21*S*)-epimer and a minor (21*R*)-epimer.

[2*S*(2*E*,4*S*,5*S*),6*S*,8*R*,9*S*,10*S*]-2-[3,5-Dimethyl-4-(triisopropylsilyl)oxy-hept-2-en-6-ynyl]-8-isopropyl-9-methyl-4-(triethylsilyl)oxy-1,7-dioxaspiro[5.5]undecan-4-one] [(17*S*,21*S*)-Spiroketal]

Yield: 380 mg (64%); $[\alpha]_D^{20}$ –19.3 (*c* 2.15, $CHCl_3$).

^{1}H NMR (400 MHz): δ = 0.61 [q, *J* = 7.5 Hz, 6 H, $(CH_3CH_2)_3Si$], 0.80 (d, *J* = 6.7 Hz, 3 H, CH_3C-24), 0.82, 0.88 [2 × d, *J* = 6.9 Hz, 6 H, $(CH_3)_2$C-26], 0.97 [t, *J* = 7.5 Hz, 9 H, $(CH_3CH_2)_3Si$], 1.07 [br m, 24 H, (*i*Pr)$_3$Si, CH_3C-12], 1.57 (m, 1 H, H-24), 1.63 (s, 3 H, CH_3C-14), 1.75 (m, 1 H, H-26), 1.76 (dd, *J* = 13.7, 3.7 Hz, 1 H, Ha-22), 1.96 (dd, *J* = 13.7, 3.0 Hz, 1 H, Hb-22), 2.03 (d, *J* = 2.4 Hz, 1 H, H-10), 2.30 (m, 5 H, H_2-16, H_2-18 and Ha-20), 2.62 (quint d, *J* = 7.0, 2.2 Hz, 1 H, H-12), 3.34 (d, *J* = 14.0 Hz, 1 H, Hb-20), 3.45 (dd, *J* = 10.0, 2.5 Hz, 1 H, H-25), 3.98 (q, *J* = 3.0 Hz, 1 H, H-23), 4.14 (d, *J* = 7.0 Hz, 1 H, H-13), 4.40 (m, 1 H, H-17), 5.45 (br t, *J* = 6.0 Hz, 1 H, H-15).

^{13}C NMR: δ = 4.8 $[(CH_3CH_2)_3Si]$, 7.0 $[(CH_3CH_2)_3Si]$, 12.2 (CH_3C-14), 12.5 $\{[(CH_3)_2CH]_3Si\}$, 13.3 (CH_3C-24), 14.0, 20.3 $[(CH_3)_2$C-26], 17.0 (CH_3C-12), 18.1 $\{[(CH_3)_2CH]_3Si\}$, 28.3 (C-26), 32.1 (C-12), 34.2, 46.4 (C-18 and C-16), 36.3 (C-24), 43.5 (C-22), 49.0 (C-20), 69.4 (C-17), 69.4 (C-10), 70.4 (C-23), 75.8 (C-25), 81.2 (C-13), 87.7 (C-11), 99.9 (C-21), 122.9 (C-15), 137.9 (C-14), 206.6 (C-19).

MS (CI, NH_3): *m*/*z* = 649 [MH^+], 595, 517, 475, 319, 223.

(17*S*,21*R*)-Spiroketal

Yield: 56 mg (9%).

^{1}H NMR (400 MHz): δ = 0.61 [q, *J* = 7.5 Hz, 6 H, $(CH_3CH_2)_3Si$], 0.80 (d, *J* = 6.8 Hz, 3 H, CH_3C-26), 0.83 (d, *J* = 6.8 Hz, 3 H, CH_3C-24), 0.98 (d, *J* = 6.8 Hz, 6 H, CH_3C-26), 0.99 [t, *J* = 7.5 Hz, 9 H, $(CH_3CH_2)_3Si$], 1.06 [br m, 24 H, (*i*Pr)$_3$Si, CH_3C-12], 1.53 (dd, *J* = 13.9, 3.3 Hz, 1 H, Ha-22), 1.60 (m, 1 H, H-24), 1.63 (s, 3 H, CH_3-14), 1.78 (sept d, *J* = 6.8, 2.0 Hz, 1 H, H-26), 1.99 (dd, *J* = 13.9, 4.6 Hz, 1 H, Hb-22), 2.03 (d, *J* = 2.0 Hz, 1 H, H-10), 2.25–2.45 (m, 2 H, H_2-16), 2.45–2.65 (m, 4 H, H_2-18, H_2-20), 2.65 (m, 1 H, H-12), 3.85 (m, 2 H, H-23 and H-25), 4.02 (m, 1 H, H-17), 4.12 (d, *J* = 7.3 Hz, 1 H, H-13), 5.39 (m, 1 H, H-15).

^{13}C NMR: δ = 4.9 [$(CH_3CH_2)_3Si$], 6.9 [$(CH_3CH_2)_3Si$], 12.1 (CH_3C-14), 12.5 {[$(CH_3)_2CH]_3Si$}, 13.2 (CH_3C-24), 14.5, 20.6 [$(CH_3)_2$C-26], 17.0 (CH_3C-12), 18.1 {[$(CH_3)_2CH]_3Si$}, 26.6 (C-26), 32.1 (C-12), 34.9, 51.0 (C-18 and C-20), 36.5 (C-24), 40.8 (C-22), 44.0 (C-16), 68.7 (C-23), 69.5 (C-10), 70.7 (C-17), 73.8 (C-25), 81.2 (C-13), 87.6 (C-11), 98.5 (C-21), 122.6 (C-15), 138.2 (C-14), 207.4 (C-19).

MS (CI, NH_3): *m/z* = 666 [MH^+ + 17], 649 [MH^+], 517, 319, 304, 223, 172.

Correlation-Equilibration of the C-21 Spiro-Center: Preparation of a 23-Deoxy Derivative of (21*S*)-25

To a solution of pure (21*S*)-**25** (45 mg, 0.07 mmol) in CH_2Cl_2 (2 mL), was added at 0 °C, HF–pyridine (~7:3, commercial) diluted in THF (1:6, v/v). This solution was added portion-wise over 24 h (0.1 mL each portion) until total consumption of starting material was observed. The reaction mixture was quenched with sat. aq $NaHCO_3$ and extracted as usual to give, after silica MPLC purification (Lichroprep Merck Art. 9336; Et_2O–PE, 20:80→75:25), the corresponding 23-O-desilylated adduct (35 mg, 95% yield). To this material (30 mg, 0.056 mmol) in THF (2 mL) was added an excess of 1,1′-thiocarbonyldiimidazole (50 mg, 0.28 mmol, 5 equiv). The reaction mixture was refluxed for 24 h. After cooling to r.t., usual work-up followed by purification of the residue by flash chromatography (Et_2O–pentane, 0:1→2:3) gave the corresponding 23-thioimidazolide (19 mg, 53% yield). To the latter thioxanthate (18 mg, 0.025 mmol) dissolved in toluene (2 mL), were added Bu_3SnH (0.032 mL, 0.1 mmol, 4 equiv) and a trace of AIBN. The resulting solution was refluxed for 2 h. After evaporation of the solvent, the residue was purified by flash chromatography (Et_2O–pentane, 0:1→3:2) to give the derivative (21*S*)-**23** as the only observable product.

Yield: 8 mg (55%).

^{1}H NMR (400 MHz): δ = 0.81, 0.88 [2 × d, *J* = 7.0 Hz, 3 H + 6 H, CH_3C-24 and $(CH_3)_2$C-26], 1.06 [br m, 24 H, $(i\text{Pr})_3Si$, CH_3C-12], 1.20–1.80 (m, 5 H, H_2-22, H_2-23 and H-24), 1.63 (s, 3 H, CH_3C-14), 1.80 (sept d, *J* = 7.0, 2.0 Hz, 1 H, H-26), 2.03 (d, *J* = 2.4 Hz, 1 H, H-10), 2.30–2.65 (m, 4 H, H_2-16 and H_2-18), 2.56 (d, *J* = 15.8 Hz, 1 H, Ha-20), 2.60 (m, 1 H, H-12), 2.95 (dd, *J* = 9.7, 2.0 Hz, 1 H, H-25), 2.98 (d, *J* = 15.9 Hz, 1 H, Hb-20), 4.13 (d, *J* = 7.2 Hz, 1 H, H-13), 4.17 (m, 1 H, H-17), 5.46 (br t, *J* = 7.0 Hz, 1 H, H-15).

MS (CI, NH_3): *m/z* = 536 [MH^+ + 17], 519 [MH^+], 475, 465, 345, 336, 327, 319.

Equilibration of (21*S*)-23 with HCl

To a solution of the preceding (17*R*,21*S*)-spiroketal (21*S*)-**23** (5 mg) in $CDCl_3$ (0.5 mL) was added a trace of HCl gas. After 12 h, the ^{1}H NMR spectrum was directly recorded and showed that the starting material was totally converted into a new product. The ^{1}H NMR data of this material, compared with those obtained for (21*R*)-**23**, resulting from the cyclization of **22** under the same conditions, were completely identical and in full agreement with the data previously obtained for the same intermediate during the synthesis of the aglycone of 22,23-dihydroavermectin b1b (**1**).

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