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Total synthesis of avermectins Part 2: Enantioselective synthesis of the C10-C25 northern fragment and final steps for the construction of the 22,23-dihydroavermectin B1b aglycone

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Summary – The total synthesis of the aglycone of 22,23-dihydroavermectin B1b involves a retrosynthetic two building-blocks approach. A Stille Pd(0) catalyzed cross-coupling reaction is carried out between a northern C10-C25 *E*-vinylstannane and a southern C1-C9 vinyl iodide. The final steps include successive removal of the carboxyl β-(trimethylsilyl)ethyl protecting group of the intermediate secoester, macrolactonization under Yonemitsu's conditions and removal of the 5-*O*-TBS protecting group. These last steps have been carried out with the aid of a relay study from commercial Ivermectin; a macrolactone opening reaction of the aglycone in the presence of $Ti(O^iPr)_4$ has been developed where the crucial $\Delta^{3,4}$ double bond as well as the configuration at C-2 were totally preserved.

avermectin / spiroketal / diastereoselection / aldolization / sulfone / homoaldolization / Hoppe reaction / hydrostannylation / palladium Stille coupling / titanium isopropoxide / transesterification / macrolactone / total synthesis

Introduction

One of the components of the marketed antiparasitic agent Ivermectin [1] is the 22,23-dihydro derivative of avermectin B1b [2]. Our program toward the synthesis of its aglycone **1** involved a two-fragment disconnection as depicted on scheme 1. The final steps of the project include a crucial Stille coupling reaction between the southern hexahydrobenzofuran moiety **2** and the northern *E*-vinylstannane **3**, as well as the subsequent macrolactone cyclization step [3].

A sequential Dieckmann-radical cyclization approach was developed to achieve the construction of the hexahydrobenzofuran nucleus [4]. A preliminary account of these results leading to the synthesis of this more complex part of avermectin was already reported in a short communication [5] and a full account of these studies has been recently reported in this journal [6]. The enantioselective synthesis of the required complex southern moiety **2** was achieved in 13 steps with an overall yield of *ca* 6%.

In the present paper we describe the synthesis of the northern fragment of 22,23-dihydroavermectin B1b as well as the last stages of the total synthesis of its aglycone **1**. These steps were carried out after a relay study from 22,23-dihydroavermectin B1a, the major component of commercial Ivermectin [7].

Synthesis of the C10-C25 moiety 3

The spirocyclic sulfone acetal **5** corresponding to the C15-C25 fragment was designed as pivotal intermediate for the synthesis of the northern C10-C25 portion **3** of **1** [8]. Chain elongation reactions were used to allow the construction of the northern moiety **3**. Aldehyde **4** was readily prepared from **5** according to a previously published procedure [9]. The addition of the two stereogenic centers at C-12 and C-13 was made through a stereoselective homoaldolization reaction according to Hoppe [10].

The first task was to prepare the key sulfone **5**. The approach adopted for the synthesis of this spiroketal sub-unit involved a stepwise double condensation at both ends of pentanedione **7**. Condensation of the homochiral halide **8** provided the only source of optical activity to the system and the subsequent aldolization step with aldehyde **6** terminated the construction of the C15-C25 fragment of **1** [11].

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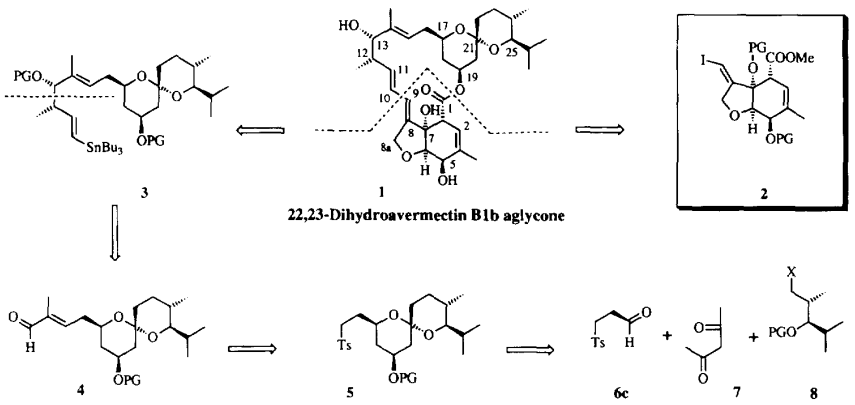
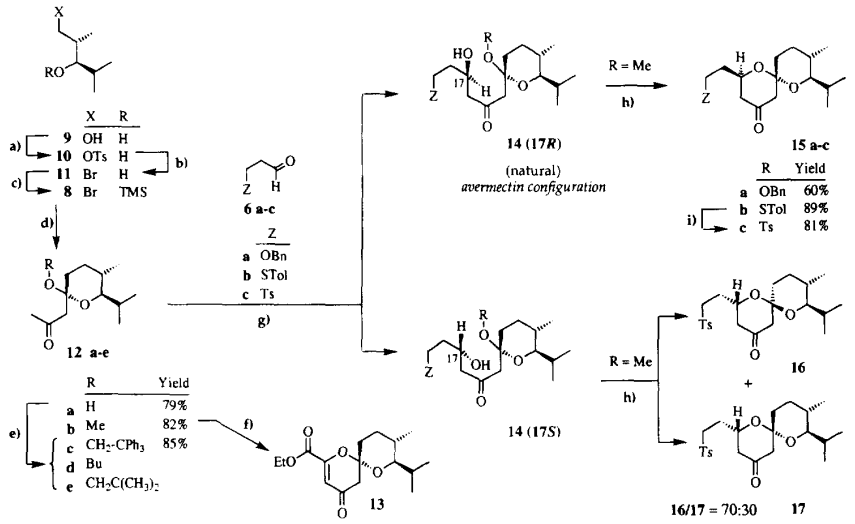


Scheme 1



a) TsCl/py, 99%; **b)** LiBr/acetone, 96%; **c)** TMSCl/HMDS, 96%; **d)** Acetylacetone dianion, then ROH/H^+; **e)** ROH, CSA, 4 Å Sieves; **f)** 1) LDA, 2) ethyl oxalate, 3) Δ, 54%; **g)** LDA then aldehyde **6a-c**, 70-90%; **h)** H^+, 60-89%; **i)** H_2O_2, *m*CPBA/CH_2Cl_2 81%.

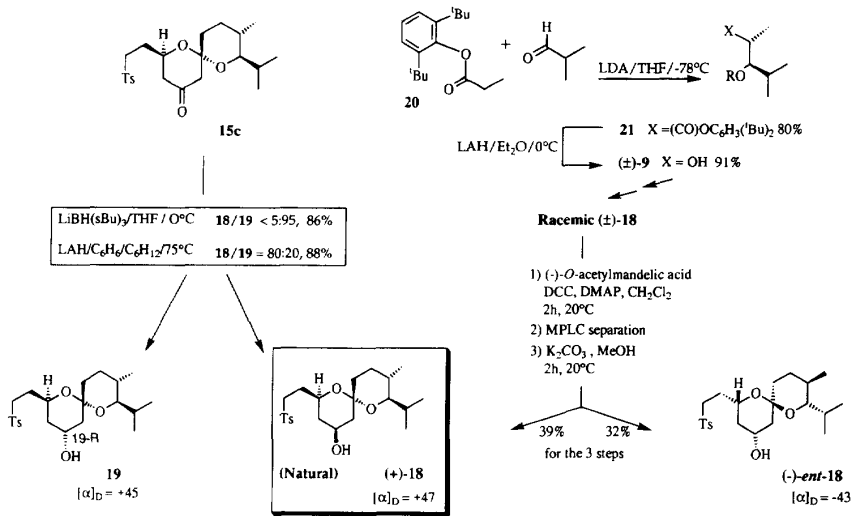
Scheme 2

Synthesis of bicyclic sulfone 18 (schemes 2 & 3)

The dianion of acetylacetone was first condensed with the homochiral silyloxy bromide **8**, easily prepared in 83% overall yield from the known (2*S*,3*R*) diol **9** [12], to give, after acidic treatment, the expected ketals **12** as single diastereomers. The diol **9** was prepared in an optically pure form through an asymmetric Sharpless epoxidation reaction. The anomeric C21 carbon of **12** was assumed to adopt the more favorable depicted configuration. The optically active hemiketal **12a** was prepared either directly from bromoalcohol **11** in 50% yield or from the trimethylsilylbromo derivative **8** in 79% yield. Methylketal **12b** was directly obtained upon acidic methanol work-up of the aldol reaction mixture. As an alternative synthetic pathway, **12b** was condensed with ethyl oxalate to give, after direct distillation of the crude acylation product, the spiroketalic ester **13** in 54% yield. This type of intermediate has been previously used by AGM Barrett *et al* during a total synthesis of milbemycins [13].

Previous work from these laboratories has shown that it was possible to govern the diastereofacial selectivity of the subsequent aldolization step using bulky acetal protecting groups [11b]. This result was anticipated assuming chelation of the lithium ion with both oxygen atoms of the ketal function, which would lead to an approach of the aldehyde electrophile from the less crowded face of the enolate anion as depicted in the figure. Such a facial differentiation would give the expected aldol product **14** with the 17*R* configuration.

To test this hypothesis, ketals **12a-e** were prepared; the bulkiest ketal **12c** was obtained upon treatment of **12a** with 2,2,2-triphenylethanol [14] under camphorsulfonic acid catalysis in the presence of molecular sieves. Some of the most significant results obtained after the



Scheme 3

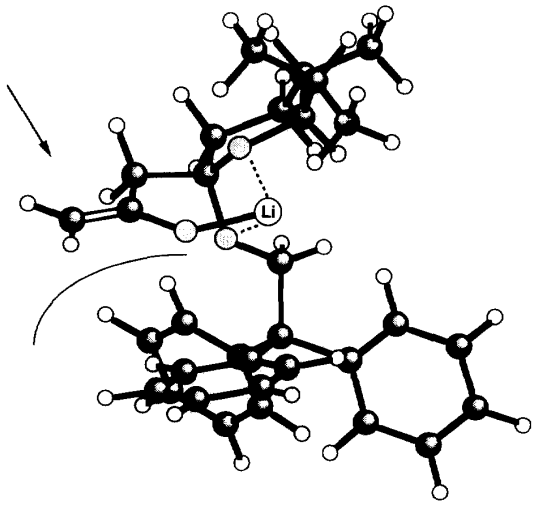


Fig. Aldol facial differenciation.

aldolization step are summarized in the table. Results obtained with β-sulfonyl aldehyde **6c** [15] were disappointing even when the bulky triphenylethyl protected ketal **12c** was used. When this ketal was condensed with the β-benzyloxy- or β-phenylthiopropionaldehyde **6a** [16] or **6b** [17], the expected **14(17*R*)** (avermectin 17-C configuration) aldol products were obtained with significant diastereocontrol of *ca* 70:30.

The configuration of the C17 center was established after conversion of the crude aldol products mixture into the corresponding spiroketals under acidic conditions. Cyclization of **14(17*R*) a-c** led to single isomers **15a-c**. The structures of **15a-c** have been tentatively assigned on the basis of i) ^{1}H and ^{13}C NMR analysis which showed all substituents to be in the more favorable equatorial orientation and ii) thermodynamic bias predicting double axial anomeric effects at the spiro center [18].

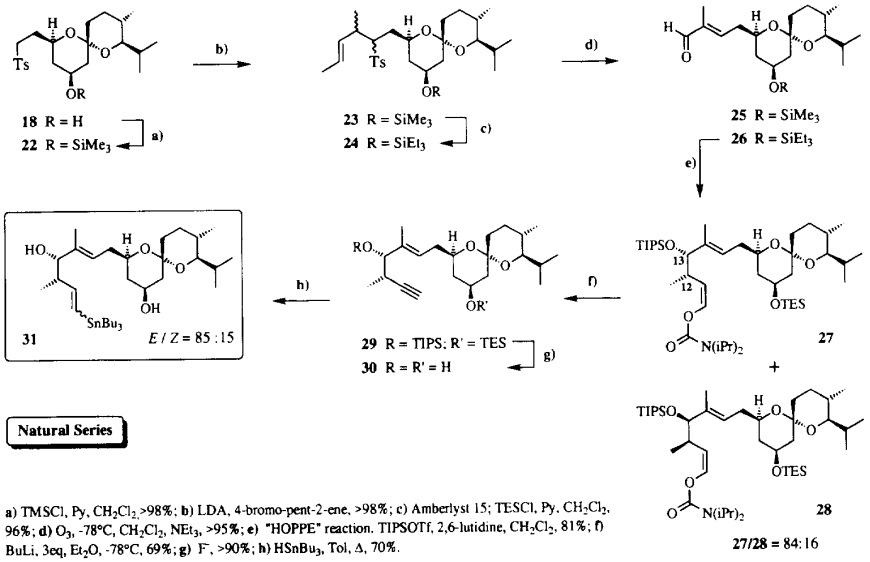
Table. Diastereoselection at C-17.

12a-e R	**6a-c** Z	**14** 17*S*/17*R*
Me	H	53/47
Me	OBn	53/47
Me	*p*-SO_2Tol	57/43
Me	*p*-STol	55/45
$CH_2C(CH_2)_3$	OBn	44/56
Bn	OBn	40/60
Bn	*p*-STol	39/61
CH_2CPh_3	H	29/71
CH_2CPh_3	*p*-SO_2Tol	56/44
CH_2CPh_3	*p*-STol	28/72

Probably due to conflicting relative stereochemical bias between favorable and unfavorable anomeric effects and axial/equatorial conformation of the C-17 side chain, the epimeric non-natural **14(17*S*)** aldol product gave, after acidic treatment, a 70:30 ratio of cyclic products **16** and **17** respectively, epimers at the spiro C-21 center.

After condensation with **12c**, β-(phenylthio)aldehyde **6b**, gave a favorable 72:28 17*R*/17*S* (avermectin configuration) diastereomeric ratio of aldols **14**, and was thus selected as a convenient synthetic precursor to spiroketal **5**. The crude aldol product **14(17*R*)c** was then converted into the bicyclic ketosulfone **15c** through acidic treatment followed by oxidation of the thioether function with *m*CPBA (55% yield from **12c**) [19].

Subsequent attempted reductions of the keto function of **15c** with $NaBH_4$ or $LiAlH_4$ in THF or diethyl ether only gave unsatisfactory ratios of equatorial/axial alcohols. The best results were obtained using $LiAlH_4$ in benzene/hexane mixture at 75°C which gave a *ca* 80:20 mixture of **18** and **19** in 88% yield (scheme 3). The observed selectivity is slightly higher than observed in similar cases [20] and probably reflects a chelation control of the hydride with the axial anomeric oxygen atom at C-19.



Scheme 4

Alternatively, reduction of **15c** with L-selectride resulted in an inverse selectivity of 95:5 (86% yield) in favour of the epimeric alcohol **19**.

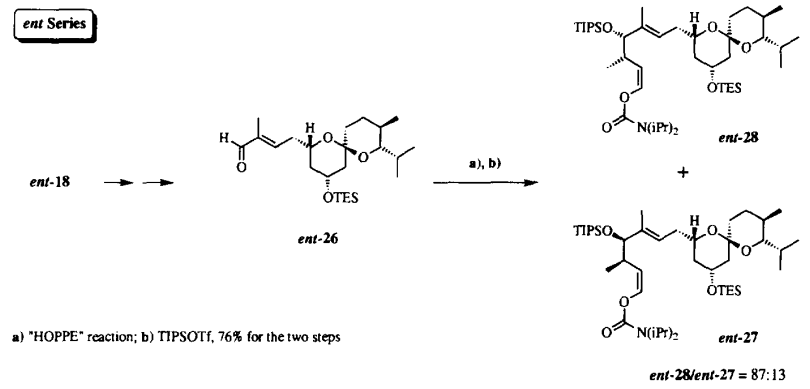
For large-scale synthesis of (+)-**18**, an alternative route was later developed involving resolution of the corresponding racemic alcohol through its mandelate ester. Racemic diol (±)-**9** was obtained by reduction of the racemic crystalline ester **21** which was prepared in good yield through Heathcock's anti-selective aldolization reaction between isobutyraldehyde and the bulky propionic ester **20** [21]. Transformation of diol (±)-**9** into (±)-**18** was carried out according to the preceding route developed for the enantiomerically pure series. The alcohol (±)-**18** was subsequently esterified with (−)-*O*-acetylmandelic acid and the diastereomeric esters separated by MPLC to give, after alkaline hydrolysis of the ester function, optically pure (+)-**18** which was identical to the same product obtained through the preceding enantioselective route.

Synthesis of the northern C10-C25 moiety of 1 (scheme 4)

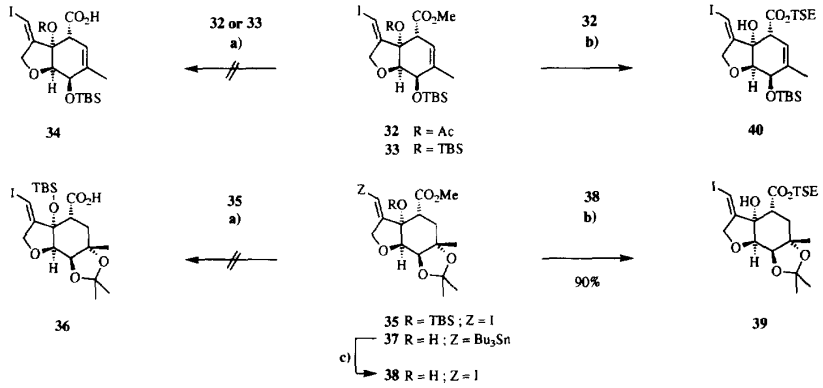
From optically (+)-**18**, aldehydes **25** and **26** were synthesized according to a reaction sequence already developed by Isobe *et al* during a synthesis of maytensinol [22]. Condensation of the anion of the protected sulfone **22** with 4-bromo pent-2-ene afforded a 1:1 diastereomeric mixture of allylic sulfones **23** in excellent yield, which were subsequently ozonized and treated with triethylamine to give the stereochemically pure *E*-aldehyde **25**. Due to its lability during this last step where variable yields of **25** were obtained, the trimethylsilyl protecting group at C-19 on **23** was then exchanged for a triethylsilyl group in nearly quantitative yield. The allylic TES-protected sulfone **24** was transformed into aldehyde **26** in 85% yield which was then submitted to the C_4-fragment elongation leading to the final C10-C25 northern moiety of 22,23-dihydroavermectin B1b.

A Hoppe enantioselective homoaldolization reaction [10] between *E*-butenyl-*N*,*N*-diisopropylcarbamate and aldehyde **26** in the presence of (−)-sparteine as homochiral complex-forming agent was addressed. Although this reaction has not yet been developed on such complex conjugated aldehydes as **26**, it was anticipated to give the expected *anti* aldol products with the correct absolute 12*S*,13*S* configuration at the newly created chiral centers. The crude product of the homoaldolization reaction was directly treated with triisopropylsilyl triflate in the presence of 2,6-lutidine to give a 85:15 mixture of the chromatographically separable diastereomeric silyl ethers **27** and **28** (scheme 4). The *Z*-vinyl carbamate **27** was then treated by an excess of BuLi to give, through a Fritsch-Buttenberg-Wiechel rearrangement [23], the acetylenic derivative **29** in 69% yield. This compound was then stannylated under equilibrating conditions ($HSnBu_3$, toluene, reflux) to give a 85:15 mixture of the corresponding *E* and *Z* vinyl stannanes. Preliminary attempts to couple this bis-silylated northern vinyl stannane with a southern vinyl iodide under Stille's conditions failed, and so we decided to prepare the unprotected vinylstannane **31** in which the bulky TIPS group at the homoallylic position was removed. The acetylenic intermediate **29** cleanly afforded the diol **30** upon treatment with tetrabutylammonium fluoride. Subsequent hydrostannylation as above gave the vinyl stannyldiol **31** as an 85:15 *E*/*Z* mixture in 70% yield.

In order to ascertain the respective stereochemistry of the two homoaldol products **27** and **28**, this homoaldolization reaction was then conducted on the enantiomeric aldehyde **ent-26** which was easily prepared from (−)-**ent-18** according to the same procedure as for **26** (scheme 5). In this case, the homoaldol reaction with *E*-crotylcarbamate in the presence of (−)-sparteine afforded the homoaldol products **ent-27** and **ent-28** with an inverse ratio of 13:87 with regard



Scheme 5



a) KOH 1M, MeOH, 120°C, 12h; b) $TMSCH_2CH_2OH$, $Ti(O\text{-}i\text{-}Pr)_4$, 90%; c) I_2, CH_2Cl_2, r.t., 30min, 90%.

Scheme 6

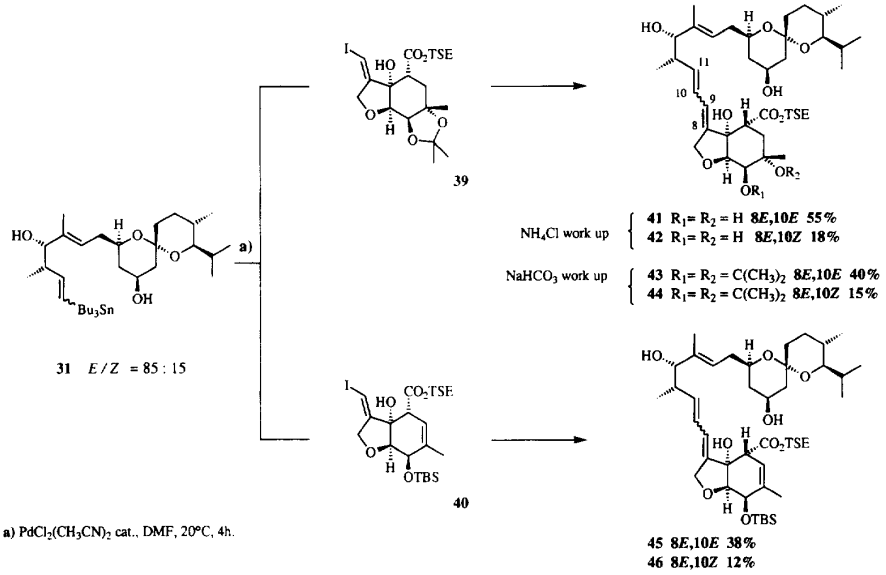
to the **27/28** enantiomers. Moreover these results indicate a quasi-exclusive reagent control of the chirality at C-12 and C-13 with no effect of the chirality of the spiroketalic aldehyde **26** (or **ent-26**). The **27/ent-27** and **28/ent-28** pairs exhibit identical NMR spectra as well as optical rotations of opposite signs, respectively, clearly indicating their respective antipodal structure and therefore the exclusive *anti* selectivity of the homoaldolization reaction.

Having reached the vinylstannane **31** corresponding to the initially designed northern moiety **3**, we now turned to the coupling reaction between the northern and southern partners.

Northern-Southern coupling reaction (schemes 6, 7)

At this stage three main operations remained to be carried out : i) the Stille's Pd(0) catalyzed coupling reaction between **2** and **3**; ii) the saponification of the carboxyl ester function at C-1 of the incipient secoavermectin and iii) the final macrolactonization step.

As depicted in scheme 6, preliminary attempts to directly remove the southern methyl esters protecting groups of **32** or **33** failed. The different tested conditions only led to degradation products or recovery of the starting material, even under saponification or thiol transesterification conditions [24]. Treatment with $(Me_3Si)_2/I_2$ [25] or NaI/PPh_3/collidine [26] also failed; no trace of **34** was detected. Assuming a possible unfavorable influence of the non-conjugated Δ^{3-4} double bond, we next turned to the acetonide precursor **35**. Again no success was encountered under any conditions tested; no trace of the saponified product **36** was detected even after drastic treatment with 1 M KOH, 12 h at 120°C. The steric hindrance at the C1-C7 centers was obviously responsible for this failure and this was verified by achieving complete saponification of the free acetonide alcohol methyl ester **38** after KOH treatment (1 h at 25°C). As the corresponding hydroxyacid was not suitable for our synthetic purposes (it required a tedious protection-deprotection sequence at the end of the synthesis to generate the Δ^{3-4} double bond through dehydration of the tertiary hydroxyl group at C-4), it was then decided to address a more convenient carboxyl protecting group where the deprotection could be triggered at a site remote from the hindered hexahydrobenzofuran nucleus. The β-(trimethylsilyl)ethyl group (TSE) was selected to protect the carboxyl at C-1; this group can be easily removed under neutral conditions upon



Scheme 7

fluoride treatment [27]. It was therefore decided to prepare the required TSE-ester by transesterification of the methyl ester function at C-1 under $Ti(O^iPr)_4$ catalysis and to take advantage of this reaction to remove the protecting group at C-7 [28]. Under these conditions, the methyl ester function of acetonide **38** was smoothly transformed into the corresponding TSE-ester **39** in excellent yield. More interestingly from a synthetic point of view, when treated under these conditions, the 7-*O*-acetyl unsaturated methyl ester **32** gave the TSE-ester **40** where the acetyl protecting group was simultaneously removed cleanly, thus avoiding a delicate late deprotection step. Neither isomerization of the Δ^3 double bond nor epimerization at C-2 was detected during the transesterification process.

These encouraging results led us to envisage a slight tactical modification of the synthetic route, which the bis-TBS ether **33**, initially designed as southern synthon, was advantageously replaced by the corresponding 7-*O*-acetyl analogue **32**, which was also described in a previous paper [6]. This derivative was converted in 90% yield into the vinyl iodide TSE-ester **40** which was then ready to be coupled under Stille conditions with the northern part **31**.

In a preliminary experiment, the northern vinylstannyl diol **31** (used as a 85:15 thermodynamic *E*/*Z* mixture) was smoothly condensed with the vinyl iodide acetonide **39** at 20°C under $PdCl_2(CH_3CN)_2$ catalysis. Under NH_4Cl hydrolytic conditions, the 8*E*,10*E* and 8*E*,10*Z* pentol TSE-secoester isomers **41** and **42** were obtained in 55 and 18% yields respectively. Alternative aqueous $NaHCO_3$ work-up afforded a mixture of the corresponding isomeric acetonide secoesters **43** and **44** in 40 and 15% yields, respectively, after purification.

We then turned to the genuine southern allylic $\Delta^{3,4}$ unsaturated synthon **40** which was coupled under the above conditions to give, after preparative TLC purification, the expected pure 8*E*,10*E* 5-*O*-TBS TSE-secoester **45** in 38% yield as well as the corresponding 8*E*,10*Z* isomer **46** in 12% yield.

The following step of the synthesis of **1** involved removal of the TSE protecting group of **45** before the final macrolactonization. Some trouble has been encountered when carrying out this reaction; treatment of **45** under well-established desilylating conditions, TBAF/THF [29], TBAF on silica gel/THF [30] or 40% aqueous HF/CH_3CN 5:95 [31] only led to decomposition products. Particularly the TBAF/THF conditions gave the C13-C25 aldehyde **4** (PG = H) probably resulting from a retroaldolization process. In view of these difficulties, it was decided to undertake at this stage a relay study from commercial Ivermectin with a triple objective : i) to test the final steps of the synthesis; ii) to develop a method allowing the opening of the macrolactone without conjugation of $\Delta^{3,4}$ double bond [32]; and iii) to avoid delicate and expensive deconjugation-epimerization operations at the end of the synthesis [33].

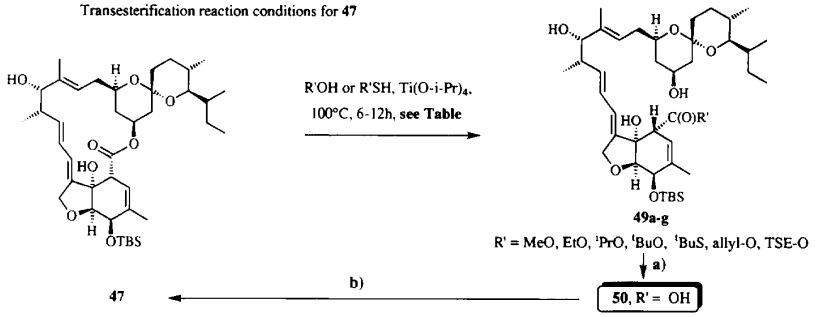
Relay study on commercial Ivermectin [34]

We envisioned opening the macrolactone under the $Ti(O^iPr)_4$ conditions previously used for the transesterification step of the southern moiety without affecting the crucial $\Delta^{3,4}$ double bond. Commercial Ivermectin, obtained as a 95:5 mixture of 22,23-dihydroavermectin B1a (*sec*-butyl at C-25) and its B1b analogue (isopropyl at C-25), was hydrolyzed [35] and the mixture of aglycones selectively silylated at the 5-OH position [36]. MPLC purification gave, in order of elution, the major 5-*O*-TBS B1a derivative **47** $[\alpha]_D = +88.5$ ($c = 2.1$, $CHCl_3$) and its minor 5-*O*-TBS B1b congener **48** $[\alpha]_D = +104$ ($c = 1.7$, $CHCl_3$) which was used for structural comparisons with our synthetic material.

Relay study

Entry	R'OH or R'SH	Secoester **49a-g**, %	Recovered starting material **47**, %
1	MeOH	**a** 58%	21%
2	EtOH	**b** 45%	18%
3	^{i}PrOH	**c** 37%	10%
4	^{t}BuOH	**d** 0%	75%
5	^{t}BuSH	**e** 20%	70%
6	CH_2=CH-CH_2-OH	**f** 56%	34%
7	$(Me)_3Si$-CH_2-CH_2-OH	**g** 61%	22%

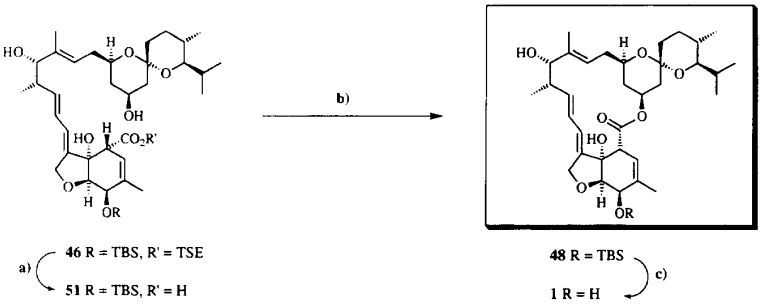
Transesterification reaction conditions for **47**



a) **49f**, dioxane $CO_2^-NH_4^+$, $PdCl_2(PPh_3)_2$, >90%; **49g**, Bu_4NF-H_2O/TsOH 3:1, THF, 20°C, >90%; b) NEt_3, DMAP, trichlorobenzoyl chloride, xylenes, 20°C, 15min, 30% yield for 2 steps.

Scheme 8

Total Synthesis



a) Bu_4NF-H_2O, TsOH, 3/1, THF, 20°C, 12h; b) NEt_3, DMAP, trichlorobenzoylchloride, xylene, 20°C,15min; c) TsOH-H_2O, MeOH, 20°C, 20min, 58%.

Scheme 9

Pure **47** was then treated with $Ti(O^{i}Pr)_4$ in the presence of various alcohols or thiols, used as a reaction medium, and the results are summarized in the table (scheme 8). As expected the reaction was very clean and only gave the corresponding secoesters. The whole southern structure was preserved and the only other isolable product was unreacted starting material. Primary alcohols gave the best results. Particularly interesting are the 61% yield obtained in the case of the TSE-secoester **49g** (assay 7) as well as the 56% yield for the allyl secoester **49f** (assay 6). Competitive transfer of the isopropyl residue was not observed except in the case of the *tert*-butyl alcohol or thiol. In contrast to transesterification reactions [27], the present secoester formation required anhydrous conditions.

It is worth noting that the allyl secoester **49f** is of synthetic importance since it allowed subsequent deprotection of the carboxyl function under neutral conditions (see below) [37].

It was then thought that, in an inverse thermodynamic esterification process, the present transesterification reaction could promote macrolactonization of the methyl secoester **49a**. When treated with $Ti(O^{i}Pr)_4$ in toluene at 120°C for several hours, **49a** gave, after chromatographic separation the expected 5-*O*-TBS B1a aglycone **47** in 22% yield after purification together with starting secoester. Here again the fragile southern moiety was not affected.

Once we had reached the TSE secoester B1a **49g**, we turned to the removal of the TSE protecting group itself. Systematic assays in the B1a series allowed clean removal of the TSE ester protecting group of **49g** under Gerlach's conditions : TBAF/*p*-TSA 3:1 in THF [38]. Under these conditions, the secoacid **50** was cleanly obtained after 12 h at ambient temperature.

The subsequent macrolactonization step was then explored (scheme 9). Attempts to cyclize the crude secoacid **50** under classical Mukaiyama's conditions only led to degradation products [39] : the only identified isolated product was the retroaldol product corresponding to **4** (PG = H, *sec*-butyl instead of isopropyl at C-25). The intermediate secoacid **50** was finally

cyclized under Yonemitsu's conditions, 2,4,6-trichlorobenzoyl chloride/Et_3N/DMAP [40], to give, a macrolactone in 33% yield from **49g**. This exhibited spectroscopic data identical to those of the original 5-*O*-TBS B1a aglycone **47**.

In parallel, the 5-*O*-TBS allyl secoester **49f** was hydrogenolyzed under mild conditions with ammonium formate under $PdCl_2(PPh_3)_2$ catalysis [36]. Further lactonization of the obtained secoacid **50** afforded, as before, the aglycone **47** in 30% yield with, again, no trace of isomerized products.

Final steps of the synthesis of 1 (scheme 9)

We then turned to the final steps of the synthesis of the 22,23-dihydroavermectin B1b aglycone **1**. Removal of the TSE protecting group of **46** was carried out under Gerlach's conditions (*vide supra*) to give the secoester **51** which was directly treated with 2,4,6-trichlorobenzoyl chloride/Et_3N/DMAP to afford, after preparative TLC, the pure corresponding 5-*O*-TBS aglycone **48** $[\alpha]_D = -6.9$ (c = 1.7, $CHCl_3$). Subsequent deprotection at C-5 under mild acidic conditions as above afforded the 22,23-dihydroavermectin B1b aglycone **1**, $[\alpha]_D = +138$ (c = 0.8, $CHCl_3$). The spectra of this synthetic material, and especially ^1H and ^{13}C NMR data, were identical to those of an authentic sample obtained by desilylation of 5-*O*-TBS B1b derivative **48** previously prepared during the above relay study from commercial Ivermectin.

Experimental section

Physical data measurements

Mass spectra were obtained on a Nermag R10-10B spectrometer *via* either direct introduction by chemical ionization with ammonia (CI, NH_3) or electronic impact (EI), GLC-MS, using a capillary column (CPSIL-5 CB, 50 m × 0.32 mm). High resolution mass spectra were recorded on a AEI-Kratos SM 50 instrument at the Organic Spectroscopy Centre, University of Pierre and Marie Curie. Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. ^1H NMR spectra were generally recorded on a Cameca 250 or on a Bruker AM 400, occasionally on a Bruker WB 80 instrument. The chemical shifts (δ) are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS) or referenced to residual chloroform (7.27 ppm). Coupling constants (J) are given in Hertz (Hz). Multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quartet) quint (quintet), sept (septet), and m (multiplet). ^{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, assigments were obtained using J-mod experiments. Infrared spectra were obtained on a Perkin-Elmer 599 model instrument (wavelengths 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

Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone; dichloromethane and chloroform were distilled from calcium hydride. Acetonitrile, triethylamine, diisopropylethylamine, dimethylformamide and pyridine were distilled from calcium hydride; pentane, hexane and petroleum ether were distilled from phosphoric anhydride and benzene, toluene and xylene (mixed) were distilled from sodium benzophenone.

Chromatography

Thin layer chromatography (TLC) was performed on precoated plates of silica gel 60F 254 (Merck, Art 7735). Flash chromatrography 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) and Merck Lichroprep R Si 60 (Art 139050 or 9336). Basic silica gel refers to $NaHCO_3$-treated silica gel Merck Art 7734 [4b].

Gas liquid chromatography was performed on a Girdel 30 gas chromatograph using a glass column (OV 101, 2% on chromosorb WHP 100-120, 2.5 m × 3.2 mm), a wide bore capillary column (BP5, SGE, 12 m × 0.52 mm), a non-polar capillary column (SE52, AML, 50 m × 0.32 mm) or a polar capillary column (BP20, SGE, 25 m × 0.32 mm).

Materials

- Silylating reagent for GLC analysis [41] : To a 25 mL flask, pyridine (10 mL), hexamethyldisilazane (4 mL) and trimethylchlorosilane (2 mL) were added. The mixture was stored under nitrogen.
- Silylation : To the product (10-20 mg), the above solution (15 drops, 200 μL) was added and the mixture was heated to 60°C for 15 min. The crude reaction mixture was directly injected into the GLC apparatus after dilution with dichloromethane (1 mL) and decantation.
- Preparation of a stock solution of LDA : To a solution of diisopropylamine (58 mL, 415 mmol) in THF (65 mL, 800 mmol) at −70°C was added dropwise butyllithium (250 mL, 1.6 M in hexane, 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.
- Diazomethane [42]
  - Preparation : To a solution of ethanol (7.5 mL), diethyl ether (22 mL), water (4 mL) and potassium hydroxide (3 g) at 50°C was added dropwise a solution of Diazald (*N*-methyl-*N*-nitro-*p*-toluenesulfonamide, 15 g, Aldrich) in diethyl ether (120 mL) using a special apparatus for diazomethane (without glass joints). The distillate containing diazomethane was collected in a cooled flask. This solution was used directly for esterifications.
  - Esterification : Under a well-ventilated hood, the acid was treated with the above solution solution until there was no further evolution of nitrogen and the solution remained pale green. Careful evaporation gave the methyl ester.
- MTPA-esters : The standard procedure of HS Mosher *et al* was followed [43]. Typically, to 10 mg of the hydroxy derivative was added 50 μL of pyridine and 50 μL of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. After standing for 1 to 15 h at 70°C, the reaction mixture was diluted with diethyl ether and directly analysed by capillary GLC (SGE, BP 20, 50 m, 150-250°C).

*Asymmetric synthesis of sulfone (+)-***18**

- *(2S,3R) 2,4-Dimethylpentane-1,3-diol* **9**

The known optically active compound **9** was obtained as described by R Baker *et al* [12] from 4-methylpent-2-enoic

acid prepared on a 100 g scale through a Doebner reaction between malonic acid and isobutyraldehyde [44].

The enantiomeric excess of the pure product was shown to be > 95% by capillary GLC analysis of its bis-MTPA ester. Mp = 35°C (hexane), $[\alpha]_D = +21$ ($c = 2.7$, CH_2Cl_2).

IR ($CHCl_3$) : 3 630, 3 400, 1 430, 1 390, 1 070, 1 030.

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.87 and 0.90 (2d, $J = 7.0$ Hz, $J = 7.0$ Hz, 6H, CH_3-4 + H_3-5), 0.97 (d, $J = 7.0$ Hz, 3H, CH_3-2), 1.84 (m, 2H, H-2 + H-4), 2.30 (m, 2H, OH), 3.34 (dd, $J = 7.5$, 3.5 Hz, 1H, H-3), 3.69 (2dd, $J = 10.5$, 7.0 Hz, 2H, CH_2-1).

MS (CI, NH_3) : m/z 150 ($MH^+ + 17$), 133 (MH^+).

Anal calc for $C_7H_{16}O_2$, 132.30 : C, 63.20, H, 12.20. Found : C, 63.44, H, 12.28.

• *(2R,3R) 1-Bromo-2,4-dimethyl-3-[(trimethylsilyl)-oxy] pentane* **8**

This reaction was carried out according to the procedure of Seebach [45].

To a cooled (−40°C) solution of *p*-toluenesulfonyl chloride (14 g, 74.4 mmol, 1.26 equiv) in dry pyridine (60 mL) was added a solution of **9** (7.85 g, 59.5 mmol, 1 equiv) in pyridine (20 mL). After 12 h at −30°C, the mixture was diluted (0°C) with an aqueous H_2SO_4 solution (4 N) and extracted with diethyl ether (4 × 200 mL). The combined organic phases were washed successively with brine, 1 M aqueous NaOH, brine then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded compound **10** as a colorless oil (21.3 g, > 99%).

• *(2S,3R) 2,4-Dimethyl-1-[(p-toluenesulfonyl)oxy] pentan-3-ol* **10**

IR ($CHCl_3$) : 3 500, 1 605, 1 475, 1 365, 850, 820.

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.83 (d, $J = 7.0$ Hz, 3H, CH_3-2), 0.94 (2d, $J = 7.0$ Hz, 6H, CH_3-4 + H_3-5), 1.62 (d, $J = 6.0$ Hz, 1H, OH), 1.78 (m, 1H, H-4), 1.89 (m, 1H, H-2), 2.47 (s, 3H, CH_3 arom), 3.27 (ddd, $J = 8.6$, 4.0, 1.0 Hz, 1H, H-3), 4.17 (2dd, $J = 9.5$, 3.7 Hz, $J = 9.5$, 5.5 Hz, 2H, CH_2-1), 7.41 (d, $J = 8.5$ Hz, 2H arom), 7.86 (d, $J = 8.5$ Hz, 2H arom).

MS (CI, NH_3) : m/z 304 ($MH^+ + 17$), 287 (MH^+).

Anal calc for $C_{14}H_{22}O_4S$, 286.39 : C, 58.72, H, 7.74. Found : C, 58.35, H, 7.83.

A solution of LiBr (50 g, 0.57 mol, 10 equiv) and tosyl derivative **10** (16.3 g, 0.57 mol, 1 equiv) in acetone (220 mL) was heated for 2 h at reflux. Acetone was removed under reduced pressure and the residue diluted with water and diethyl ether. Decantation of the organic phase and re-extraction with diethyl ether gave a crude residue which was distilled to afford bromo compound **11** (10.7 g, 96%).

• *(2S,3R) 1-bromo-2,4-dimethylpentan-3-ol* **11**

Bp = 100°C/0.01 mmHg.

IR ($CHCl_3$) : 3 475, 1 380, 1 365.

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.90 (d, $J = 7.0$ Hz, 3H, CH_3-2), 1.01 (2d, $J = 7.0$ Hz, 6H, CH_3-4 + H_3-5), 1.62 (d, $J = 6.0$ Hz, 1H, OH), 1.89 (m, 1H, H-4), 1.92 (m, 1H, H-2), 3.35 (dd, $J = 8.5$, 4.5 Hz, 1H , H-3), 3.68 (2dd, $J = 10.0$, 3.5 Hz, $J = 10.0$, 5.5 Hz, 2H, CH_2-1).

Anal calc for $C_7H_{15}OBr$, 195.11 : C, 43.09, H, 7.75. Found : C, 42.94, H, 7.74.

To a solution of **11** (11.09 g, 56.9 mmol, 1 equiv), in pyridine (5.3 mL) and pentane (25 mL), was added HMDS (5.8 mL, 28.5 mmol, 0.5 equiv) and TMSCl (3.6 mL, 28.5 mmol, 0.5 equiv). After refluxing for 1 h under N_2, the mixture was cooled, diluted with water and extracted with pentane. Distillation of the crude residue led to the title compound, **8** (14.9 g, 96.5%).

8 : bp = 70-78°C/0.3 mmHg. $[\alpha]_D = -39$ ($c = 1.5$, $CHCl_3$).

IR ($CHCl_3$) : 2 970, 2 880, 1 465, 1 385, 1 060, 880, 845.

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.16 (s, 9H, $3CH_3$, $Si(CH_3)_3$), 0.84 (d, $J = 7.0$ Hz, 3H, CH_3-2), 0.94 and 1.01 (2d, $J = 7.0$ Hz, 6H, CH_3-4 + H_3-5), 1.77 (d, $J = 6.0$ Hz, 1H, H-4), 1.88 (m, 1H, H-2), 3.40 (dd, $J = 7.5$, 3.5 Hz, 1H, H-3), 3.58 (dd+d, $J = 4.2$, 1.5 Hz, $J = 4.2$ Hz, 2H, CH_2-1).

MS (CI, NH_3) : m/z 269 ($MH^+ + NH_3 - 15$), 267 (MH^+), 179, 177.

Anal calc for $C_{10}H_{23}OBrSi$, 267.29 : C, 44.94, H, 8.67. Found : C, 45.21, H, 8.70.

• *(2R,5S,6R) 1-(2-Hydroxy-6-isopropyl-5-methyl tetrahydro-2H-pyran-2-yl)propan-2-one* **12a**

■ *From bromo-alcohol* **11**

To a cooled (−78°C) solution of LDA (1.1 M sol in hexane, 20 mL, 22 mmol, 6 equiv) was added a solution of acetylacetone **7** (950 μL, 9.25 mmol, 2.5 equiv) in THF (5 mL). The temperature was then allowed to reach 0°C and after 15 min, the dianion solution was cooled to −78°C and bromo-alcohol **11** (720 mg, 3.7 mmol, 1 equiv) in THF (2 mL) was added *via* a syringe. After 1 h at room temperature, the mixture was poured in an aqueous saturated NH_4Cl (0°C) solution, and extracted with diethyl ether (×3). The combined organic phases were washed (H_2O, NaCl), dried ($MgSO_4$) and the solvent was evaporated. Chromatography and crystallization afforded pure **12a** (2.4 g, 50%).

■ *From bromo-silylether* **8**

To a cooled (−78°C) solution of diisopropylamine (29.5 mL, 210 mmol) was added a 1.6 M solution of BuLi in hexane (125 mL, 200 mmol). The temperature was then allowed to reach 0°C (20 min), the solution was cooled down to −78°C. Acetylacetone **7** (9.95 mL, 97 mmol, 2.5 equiv) was then slowly added at −78°C then the solution was allowed to reach room temperature and after 1 h the dianion solution was cooled to −78°C. HMPA (17.5 mL, 100 mmol) and bromo-silylether **8** (12.9 g, 48.4 mmol) in THF (20 mL) were sequentially added *via* a syringe. After stirring for 20 min at −78°C and 1 h at room temperature, the mixture was poured into an aqueous saturated NH_4Cl (0°C) solution, and extracted with diethyl ether (×3). The combined organic phases were washed (H_2O, NaCl), dried ($MgSO_4$) and the solvent was evaporated.

The crude residue in a 4:1 mixture of THF/H_2O (200 mL/50 mL) was then treated with citric acid (2 g) for 3 days at room temperature. After partial removal of the solvent *in vacuo*, the mixture was diluted with aqueous $NaHCO_3$ and extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to give a crude residue which was purified by chromatography on silica gel (pentane/diethyl ether mixtures) to give pure **12a** which crystallized upon drying (8.16 g, 79%). mp = 52-54°C. $[\alpha]_D = +112$ ($c = 2.0$, $CHCl_3$).

IR ($CHCl_3$) : 3 460, 2 965, 2 940, 2 880, 1 700, 1 460, 1 420, 1 385, 1 365, 1 305, 1 175, 1 115, 1 020, 975.

^1H NMR ($CDCl_3$, 250 MHz), *avermectin numbering* δ : 0.77 (d, $J = 7.0$ Hz, 3H, CH_3-26), 0.78 (d, $J = 6.5$ Hz, 3H, CH_3-26), 0.86 (d, $J = 7.0$ Hz, 3H, CH_3-24), 1.48 (m, 4H, CH_2-22 + CH_2-23), 1.71 (td, $J = 17.0$, 3.0 Hz, 1H, H-24), 1.85 (dquint, $J = 8.0$, 2.5 Hz, 1H, H-26), 2.23 (s, 3H, CH_3-CO), 2.44 (d, $J = 14.5$ Hz, 1H, Ha-20), 2.88 (d, $J = 14.5$ Hz, 1H, Hb-20), 3.39 (dd, $J = 10.0$, 2.0 Hz, 1H, H-25), 4, 60 (d, $J = 2.0$ Hz, 1H, OH).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 13.99 (CH_3-26), 16.86 (CH_3-26), 19.92 (CH_3-24), 22.67 (C-23), 22.71 (C-26), 31.34 (C-24), 32.50 (C-18), 34.90 (C-22), 52.21 (C-20), 78.35 (C-25), 95.62 (C-21), 210.31 (C-19).

MS (IC, NH_3) : m/z 215, 198, 197, 179, 175, 174, 164, 158, 157.

Anal calc for $C_{12}H_{22}O_3$, 214.30 : C, 67.26, H, 10.35. Found : C, 66.85, H, 10.35

• *(2R,5S,6R) 1-[6-Isopropyl-2-methoxy-5-methyl tetrahydro-2H-pyran-2-yl] propan-2-one* **12b**

To a cooled (−78°C) solution of diisopropylamine (195 mL, 1.15 mol) in THF (600 mL) was added 770 mL of *n*BuLi (1.5 M, 1.15 mol). After 30 min the temperature was allowed to reach −20°C. The solution was then cooled to −78°C and acetylacetone **7** (53 mL, 0.512 mol) was added. Temperature was kept for 30 min at −78°C and then allowed to reach 20°C. After 30 min, the dianion solution was cooled to −78°C and bromo-derivative **8** (68.5 g, 0.256 mol) in THF/HMPA (100 mL/110 mL, 25 mmol, 2.5 equiv) was added *via* a syringe. After 1 h at −78°C, the temperature was allowed to reach 20°C over 12 h. The mixture was poured into a saturated aqueous NH_4Cl solution (0°C), and extracted with diethyl ether to give 64 g of (2*R*,5*S*,6*R*) 2,4-dimethyl-3-[(trimethylsilyl)oxy] decane-7,9-dione as a yellow oil.

IR ($CHCl_3$) : 2 970, 2 880, 1 730, 1 705, 1 615, 1 465, 1 385, 1 090.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : (enol form/keto form = 75:25) 0.13 (s, 9H, $3CH_3$, $(CH_3)_3$-Si), 0.88 (m, 9H, $3CH_3$), 1.33 (m, 1H, Ha-5), 1.60 (m, 1H, H-4), 1.77 (m, 1H, H-2), 1.85 (m, 1H, Hb-5), 2.06 (s, 2.25 H, H_3-10 enol form), 2.24 (s, 0.75 H, H_3-10 keto form), 2.27 (2ddd, J = 15.0, 10.0, 6.5 Hz, J = 15.0, 10.0, 5.5 Hz, 2H, CH_2-6), 3.10 (m, 1H, H-3), 3.58 (s, 0.5H, CH_2-8 keto form), 5.51 (s, 0.75H, H-8 enol form), 15.51 (s, 0.75H, OH-enol).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 0.71, 16.85, 16.89, 17.73, 17.79, 20.26, 24.72, 27.33, 30.74, 35.68, 36.04, 41.71, 57.68, 82.70, 99.43, 191.11, 194.36, 201.71, 204.05.

The crude residue obtained above (64 g, 0.223 mol) was dissolved in MeOH (1 L), and treated for 4 h at room temperature with citric acid (71 g, 0.336 mol, 1.5 equiv). The mixture was then diluted with a saturated aqueous $NaHCO_3$ solution and extracted with diethyl ether. The crude residue was distilled to afford 40.8 g of title product **12b** as a colorless oil in 82% yield for the two steps.

12b : bp = 86°C/0.1 mmHg. $[\alpha]_D$ = +16.4 (c = 2.7, CH_2Cl_2).

IR ($CHCl_3$) : 3 005, 2 970, 2 880, 1 710, 1 465, 1 385 1 090, 1 050, 1 010, 970.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.79 and 0.83 (2d, J = 7.0 Hz, 6H, $2CH_3$-26), 1.03 (d, J = 7.0 Hz, 3H, CH_3-24), 1.50 (m, 3H, CH_2-23 + H-24), 1.68 (m, 2H, CH_2-22), 1.91 (d sept, J = 6.75, 2.25 Hz, 1H, H-26), 2.24 (s, 3H, CH_3CO), 2.44 (d, J = 12.5 Hz, 1H, Ha-20), 2.63 (d, J = 12.5 Hz, 1H, Hb-20), 3.12 (dd, J = 9.5, 2.25 Hz, 1H, H-25), 3.24 (s, 3H, O-CH_3).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 14.06 (CH_3-26), 17.00 (CH_3-26), 20.13 (CH_3-24), 27.76 (C-23), 28.06 (C-26), 31.02 (C-24), 31.59 (C-18), 33.05 (C-22), 47.53 (O-CH_3), 50.14 (C-20), 79.41 (C-25), 97.65 (C-21), 206.48 (C-19).

MS (IC, NH_3) : m/z 199, 198, 197, 179.

Anal calc for $C_{13}H_{24}O_3$, 228.33 : C, 68.38, H, 10.59. Found : C, 68.48, H, 10.62.

• *(2R,5S,6R) 1-[6-Isopropyl-5-methyl-2-(2,2,2-triphenylethoxy)-tetrahydro-2H-pyran-2-yl] propan-2-one* **12c**

Triphenylethanol (mp 104-105°C, ether/hexane) was prepared through condensation of formaldehyde (obtained from depolymerization of paraformaldehyde) onto the anion of triphenylmethane (BuLi, THF) using a described procedure (40-50% yield) [14].

Hemiacetal **12a** (0.53 g, 2.48 mmol) was dissolved in 7.5 mL anhydrous benzene, then treated with triphenyl ethanol (1.0 g, 3.6 mmol, 1.5 equiv), 1 g of activated 4 Å molecular sieves and 24 mg (5 mol%) of PTSA. After stirring for 3 h at room temperature, anhydrous sodium hydrogen carbonate was added to the reaction mixture which, after 30 min stirring, was directly poured over a short silica pad pretreated with $NaHCO_3$. Elution with pentane/diethyl ether fractions gave the expected triphenylethyl acetal **12c** (994 mg) in 85% yield. mp = 143-145°C (hexane/diethyl ether). $[\alpha]_D$ = +122 (c = 2.25, $CHCl_3$).

IR ($CHCl_3$) : 3 090, 3 060, 2 970, 2 940, 2 880, 1 705, 1 600, 1 490, 1 460, 1 450, 1 380 1 370, 1 310, 1 170, 1 120-1 110.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.56 (d, J = 6.0 Hz, 3H, CH_3), 0.74 (d, J = 6.0 Hz, 3H, CH_3), 0.92 (d, J = 7.0 Hz, 3H, CH_3), 1.24 (m, 3H), 1.55 (m, 2H), 1.67 (d sept, J = 4.75, 2.2 Hz, 1H, H-26), 2.21 (s, 3H, CH_3-18), 2.29 (d, J = 12.0 Hz, 1H, H-20a), 2.51 (dd, J = 9.5, 2.0 Hz, 1H, H-25), 3.18 (d, J = 12.0 Hz, 1H, H-20b), 4.24 (d, J = 9.0 Hz, 1H, H-1'a), 4.66 (d, J = 9.0 Hz, 1H, H-1'b), 7.22 (m, 15H, H arom).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 14.3 (CH_3-26), 16.95 (CH_3-26), 20.17 (CH_3-24), 27.52 (C-23), 28.02 (C-26), 30.82 (C-24), 32.05 (C-18), 33.24 (C-22), 51.18 (C-18), 56.79 (C-20), 66.19 (C-1'), 79.13 (C-25), 98.17 (C-21), 126.13, 127.84, 129.54, 145.69 (C arom), 207.43 (C-19).

MS (IC, NH_3) : m/z 488 (MH^+ + NH_3), 471 (MH^+), 394, 377, 292, 257, 243, 214.

Anal calc for $C_{32}H_{38}O_3$, 470.62 : C, 81.66, H, 8.14. Found : C, 81.36, H, 8.13.

• *(6S,8R,9S) Methyl 8-isopropyl-9-methyl-4-oxo-1,7-dioxaspiro[5.5]undec-2-ene-2-carboxylate* **13**

To a cooled (−78°C) stock solution of LDA (1.1 M, 10 mL, 11 mmol, 1.1 equiv) was added *via* a cannula a cooled (−78°C) solution of the acetal **12b** (2.28 g, 10 mmol, 1 equiv) in THF (10 mL). After 20 min the resulting solution was added dropwise *via* a cannula to a solution of diethyl oxalate (2.29 g, 20 mmol, 1 equiv) in THF (10 mL) at −78°C. After stirring for 3 h at −10°C, the orange solution was poured at 0°C in a saturated aqueous NH_4Cl solution (25 mL), and extracted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude residue was distilled (250°C, 0.1 mmHg) to give the expected derivative **13** which was purified by MPLC eluted with pentane/diethyl ether fractions from 95:5 to 60:40 (1.76 g, 54% yield). $[\alpha]_D$ = +26.1 (c = 2.7, CH_2Cl_2).

IR ($CHCl_3$) : 3 015, 1 740, 1 680, 1 605, 1 460, 1 385, 816.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.77 (2d, J = 7.0 Hz, 6H, $2CH_3$-26), 0.84 (d, J = 7.0 Hz, 3H, CH_3-24), 1.35 (t, J = 7.0 Hz, 3H, CH_3-CH_2-O), 1.70 (m, 5H, CH_2-22 + CH_2-23 + H-26), 2.10 (dt, J = 10.0, 2.0 Hz, 1H, H-24), 2.64 (2d, J = 17.0 Hz, 2H, CH_2-20), 3.22 (dd, J = 10.0, 2.0 Hz, 1H, H-25), 4.33 (m, 2H, CH_2-O), 6.24 (s, 1H, H-18).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 13.37 (CH_3-CH_2-O), 13.63 (CH_3-26), 16.61 (CH_3-26), 19.62 (CH_3-24), 27.08 (C-23), 27.58 (C-26), 30.66 (C-24), 33.47 (C-22), 47.03 (C-20), 61.71 (O-CH_2-CH_3), 80.90 (C-25), 104.26 (C-21),

109.29 (C-18), 154.36 (C-17), 161.72 (C-16), 192.67 (C-19).

MS (CI, NH_3) : m/z 297 (MH^+).

• *Aldolization reaction between methylketones* **12** *and aldehydes* **6** *: Study of the diastereoselectivity at C-17*

■ *3-Substituted propanal*

3-(Benzyloxy) propanal **6a** and 3-(*p*-tolylthio) propanal **6b** were prepared as described in references [16] and [17] respectively.

3-(*p*-toluenesulfonyl) propanal **6c** was prepared as follows, according to reference [15]. To a solution of *p*-toluenesulfinic acid sodium salt (44.5 g, 0.25 mol) in a mixture of acetic acid (14.3 mL) and water (250 mL) was added acrolein (14.7 g, 0.26 mol). The reaction mixture was stirred for 48 h at room temperature, and then treated with water (60 mL) and extracted twice with dichloromethane. The combined organic phases were washed with water, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (diethyl ether/ethyl acetate from 100:0 to 30:70) to give sulfone **6c** in 78% yield (41.5 g).

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 2.44 (s, 3H, CH_3-7'), 2.92 (t, J = 7.0 Hz, 2H, CH_2-2), 3.40 (t, J = 7.0 Hz, 2H, CH_2-3), 7.35 (d, J = 8.0 Hz, 2H, H-2' + H-6'), 7.74 (d, J = 8.0 Hz, 2H, H-3' + H-5'), 9.70 (s, 1H, H-1).

■ *Aldolization reactions*

– *General procedure* : To a cooled (−78°C) solution of LDA (1-1.25 equiv) in THF (1 mL) was added a cooled (−78°C) solution of the acetal **12a-c** (0.25 mmol) in THF (1 mL). After stirring for 30 min, the required propanal derivative **6a-c** (1.5 equiv) in THF (1 mL) was added dropwise. After disappearance of the starting material (TLC monitoring), the reaction mixture was poured into an ice-cooled saturated aqueous NH_4Cl solution, and extracted (×3) with diethyl ether. The combined organic phases were washed with brine, dried ($MgSO_4$), and the solvent was evaporated to give the expected aldol products **14**.

– *Analytical reactions* : All assays were performed on a 0.25 mmol scale according to the general procedure. The crude extracts were directly analyzed by silica gel HPLC (diisopropyl ether/isooctane mixtures, UV detection at 265 nm) and the results are reported in the table. For each assay, the **14**-17*R* isomer was treated in acidic media and purified by chromatography to give the corresponding spiroketal derivatives **15a-c**.

– *Preparative scale* : the crude aldolization mixture either directly underwent spirocyclization or was purified before the acidic treatment.

• *[4*R*(2*R*,5*S*,6*R*)] 6-Benzyloxy-4-hydroxy-1-[(6-isopropyl-2-methoxy-5-methyl) tetrahydro-2H-pyran-2-yl] hexan-2-one* **14**-*(17*R*, Z=Bn, R=Me)*

*[4*S*(2*R*,5*S*,6*R*)] 6-Benzyloxy-4-hydroxy-1-[(6-isopropyl-2-methoxy-5-methyl) tetrahydro-2H-pyran-2-yl] hexan-2-one* **14**-*(17*S*, Z=Bn, R=Me)*

Condensation of acetal **12b** (1.14 g, 5 mmol, 1 equiv) with (benzyloxy)propanal **6a** (1.23 g, 7.5 mmol, 1.5 equiv) under the general conditions (2 h at −78°C), followed by chromatography on silica gel (pentane/diethyl ether) afforded the two title isomers 17*R* (410 mg, 19%) and 17*S* (668 mg, 31%).

14-(17*R*, Z=Bn, R=Me) : $[\alpha]_D$ = +8.7 (c = 2.7, CH_2Cl_2).

IR ($CHCl_3$) : 3 500, 2 980, 1 720, 1 500, 1 460, 1 380, 1 110.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.79, 0.84, 1.02 (3d, J = 7.0 Hz, 9H, $2CH_3$-26 + CH_3-24), 1.49 (m, 3H, CH_2-23 + H-24), 1.69 (m, 2H, CH_2-22), 1.76 (m, 2H, CH_2-16), 1.9 (d sept, J = 7.0, 2.5 Hz, 1H, H-26), 2.69 (2d, J = 13.0 Hz, 2H, CH_2-20), 2.74 (2dd, J = 18.0, 4.25 Hz, J = 18.0, 8.0 Hz, 2H, CH_2-18), 3.13 (dd, J = 9.25, 2.0 Hz, 1H, H-25), 3.23 (s, 3H, O-CH_3), 3.34 (d, J = 3.0 Hz, 1H, OH), 3.66 (m, 2H, CH_2-15), 4.26 (m, 1H, H-17), 4.51 (s, 2H, O-CH_2-Ph), 7.34 (m, 5H, H arom).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 14.20 (CH_3-26), 17.04 (CH_3-26), 20.14 (CH_3-24), 27.77 (C-23), 28.07 (C-26), 31.04 (C-24), 33.27 (C-16), 35.97 (C-22), 47.44 (O-CH_3), 49.98 (C-18), 50.84 (C-20), 65.89 (C-17), 67.57 (C-15), 72.95 (O-CH_2-Ph), 79.48 (C-25), 97.65 (C-21), 127.41, 127.43 (2C), 128.17 (2C), 137.98, 208.86 (C-19).

MS (IC, NH_3) : m/z 316 (MH^+ – MeOH).

14-(17*S*, Z=Bn, R=Me) : $[\alpha]_D$ = +8.7 (c = 2.7, CH_2Cl_2).

IR ($CHCl_3$) : 3 500, 2 980, 1 720, 1 500, 1 460, 1 380, 1 110.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.78, 0.81, 1.02 (3d, J = 7.0 Hz, 9H, $2CH_3$-26, CH_3-24), 1.50 (m, 3H, CH_2-23 + H-24), 1.68 (m, 2H, CH_2-22), 1.75 (m, 2H, CH_2-16), 1.90 (d sept, J = 7.0, 2.5 Hz, 1H, H-26), 2.68 (2d, J = 12.5 Hz, 2H, CH_2-20), 2.76 (2dd, J = 17.7, 8.1 Hz, J = 17.7, 3.7 Hz, 2H, CH_2-18), 3.13 (dd, J = 10.0, 2.0 Hz, 1H, H-25), 3.21 (s, 3H, O-CH_3), 3.42 (d, J = 3.0 Hz, 1H, OH), 3.66 (m, 2H, CH_2-15) 4.24 (m, 1H, H-17), 4.51 (s, 2H, O-CH_2-Ph), 7.34 (m, 5H, H arom).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 14.05 (CH_3-26), 16.88 (CH_3-26), 20.06 (CH_3-24), 27.62 (C-23), 27.89 (C-26), 30.91 (C-24), 33.04 (C-16), 35.92 (C-22), 47.23 (O-CH_3), 49.85 (C-18), 50.80 (C-20), 65.89 (C-17), 67.33 (C-15), 72.71 (O-CH_2-Ph), 79.26 (C-25), 97.58 (C-21), 127.22 (3C), 127,99 (2C), 137.91, 208.71 (C-19).

MS (IC, NH_3) : m/z 316 (MH^+ – MeOH).

• *[4*R*(2*R*,5*S*,6*R*)] 4-Hydroxy-1-[(6-isopropyl-2-methoxy-5-methyl) tetrahydro-2*H*-pyran-2-yl]-6-(*p*-tolylthio) hexan-2-one* **14**-*(17*R*, Z=*p*-tolylthio, R=Me)*

*[4*S*(2*R*,5*S*,6*R*)] 4-Hydroxy-1-[(6-isopropyl-2-methoxy-5-methyl) tetrahydro-2*H*-pyran-2-yl]-6-(*p*-tolylthio) hexan-2-one* **14**-*(17*S*, Z=*p*-tolylthio, R=Me)*

Acetal **12b** (1.73 g, 7.5 mmol, 1 equiv) and 2-(*p*-tolylthio)propanal **6b** (1.92 g, 1.4 equiv) were condensed under the general aldolization conditions (10 min at −78°C). MPLC purification on silica gel afforded the two title isomers 17*R* (370 mg, 17%) and 17*S* (668 mg, 27%).

14-(17*R*, Z=*p*-tolylthio, R=Me) : $[\alpha]_D$ = +90 (c = 2.0, $CHCl_3$).

IR ($CHCl_3$) : 3 500, 3 000, 2 940, 2 880, 1 700, 1 500, 1 460, 1 380, 1 370, 1 310, 1 100-1 000, 970, 810.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.79 (d, J = 6.0 Hz, 3H, CH_3), 0.83 (d, J = 6.0 Hz, 3H, CH_3), 1.02 (d, J = 7.0 Hz, 3H, CH_3), 1.35-1.82 (m, 7H), 1.90 (d sept, J = 7.0, 2.0 Hz, 1H, H-26), 2.33 (s, 3H, H arom), 2.48 (d, J = 13.0 Hz, 1H, Ha-20), 2.67 (dd, J = 18.0, 3.5 Hz, 1H, Ha-18), 2.78 (dd, J = 18.0, 8.5 Hz, 1H, Hb-18), 2.90 (d, J = 13.0 Hz, 1H, Hb-20), 2.90-3.18 (m, 4H), 3.24 (s, 3H, CH_3-O), 4.19 (m, 1H, H-17), 7.13 (d wide, J = 8.0 Hz, 2H, H arom), 7.30 (d wide, J = 8.0 Hz, 2H, H arom).

MS (IC, NH_3) : m/z 394 (MH^+ – 15), 377, 359, 197, 181.

Anal calc for $C_{23}H_{36}O_4S$, 408.59 : C, 67.61, H 8.88. Found C, 67.72, H, 8.79.

14-(17*S*, Z=*p*-tolylthio, R=Me) : $[\alpha]_D$ = +104 (c = 2.0, $CHCl_3$).

IR ($CHCl_3$) : 3 500, 3 000, 2 970, 2 940, 2 880, 1 700, 1 460, 1 380, 1 360, 1 310, 1 270, 1 100-1 000, 970, 810.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.77 (d, J = 7.0 Hz, 3H, CH_3), 0.79 (d, J = 6.0 Hz, 3H, CH_3), 1.00 (d, J = 7.0 Hz, 3H, CH_3), 1.31-1.81 (m, 7H), 1.90 (d sept, J = 7.0, 2.0 Hz, 1H, H-26), 2.30 (s, 3H, H arom), 2.41 (d, J = 12.0 Hz, 1H, Ha-20), 2.56 (dd, J = 18.0, 9.5 Hz, 1H, Ha-18), 2.89 (dd, J = 18.0, 2.5 Hz, 1H, Hb-18), 2.95 (d, J = 12.0 Hz, 1H, Hb-20), 2.95-3.16 (m, 3H, H-25 + H_2-5), 3.24 (s, 3H, CH_3-O), 3.30 (dd, J = 3.0, 1.0 Hz, 1H, O-H), 4.19 (m, 1H, H-17), 7.14 (d wide, J = 8.0 Hz, 2H, H arom), 7.30 (d wide, J = 8.0 Hz, 2H, H arom).

MS (IC, NH_3) : m/z 377 (MH^+ - 15-17), 235, 197.

• *[4RS(2R,5S,6R)] 4-Hydroxy-1-[(6-isopropyl-2-methoxy-5-methyl) tetrahydro-2H-pyran-2-yl]-6-(*p*-toluenesulfonyl)hexan-2-one* **14**-*(17RS, Z=Ts, R=Me)*

Acetal ketone **12b** (0.91 g, 4 mmol, 1 equiv) and 2-(*p*-toluenesulfonyl)propanal **6c** (1.19 g, 5.6 mmol, 1.4 equiv) were condensed under the general aldolization conditions, 2 h at −78°C, to give a mixture of the two title isomeric aldol products (2.169 g, 17*R*/17*S* = 43:57) which directly underwent the subsequent acid treatment (see preparation of **15c** below).

• *(2R,6S,8R,9S) 2-[2-(Benzyloxy)ethyl]-8-isopropyl-9-methyl-1,7-dioxaspiro[5.5]undecan-4-one* **15a**

To an ice-cooled HCl/H_2O/THF (5 mL, 1:5:20) solution was added acetal **14a** (17*R*, Z = Bn, R = Me) (150 mg, 0.4 mmol, 1 equiv). After stirring for 2 h, the mixture was extracted with diethyl ether, washed with dilute aqueous $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue chromatographed on silica gel to give the title compound **15a** in 60% yield (86 mg). $[\alpha]_D$ = +6 (c = 2.7, CH_2Cl_2).

IR ($CHCl_3$) : 3 010, 2 980, 1 720, 1 460, 1 380, 1 110.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.76, 0.80, 0.84 (3d, J = 7.0 Hz, 9H, $2CH_3$-26, CH_3-24), 1.50-1.80 (m, 5H, CH_2-22 + CH_2-23 + H-24), 1.78 (d sept, J = 7.0, 2.0 Hz, 1H, H-26), 1.87 (m, 2H, CH_2-16), 2.26 (dd, J = 15.0, 11.0 Hz, 1H, Ha-18), 2.28 (ddd, J = 15.0, 3.1, 1.5 Hz, 1H, Hb-18), 2.35 (d, J = 14.5 Hz, 1H, Ha-20), 2.37 (dd, J = 14.5, 1.5 Hz, 1H, Hb-20), 3.09 (dd, J = 9.5, 2.0 Hz, 1H, H-25), 3.64 (dt, J = 9.0, 5.0 Hz, 1H, Ha-15), 3.68 (dt, J = 9.0, 6.5 Hz, 1H, Hb-15), 4.17 (m, 1H, H-17), 4.50 (2d, J = 12.0 Hz, 2H, O-CH_2-Ph), 7.33 (m, 5H, H arom).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 13.87 (CH_3-26), 17.30 (CH_3-26), 19.95 (CH_3-24), 28.14 (C-26), 28.19 (C-23), 30.92 (C-24), 35.27 (C-16), 36.23 (C-22), 46.94 (C-18), 51.72 (C-20), 65.12 (C-17), 66.27 (C-15), 73.17 (O-CH_2-Ph), 78.67 (C-25), 98.69 (C-21), 127.52, 127.64 (2C), 128.23 (2C), 138.07, 206.04 (C-19).

MS (IC, NH_3) : m/z 361 (MH^+).

• *(2R,6S,8R,9S) 8-Isopropyl-9-methyl-2-[2-(*p*-tolylthio)ethyl]-1,7-dioxaspiro[5.5]undecan-4-one* **15b**

The aldol product **14**-(17*R*, Z=*p*-tolylthio, R=Me) (860 mg, 2.10 mmol) was dissolved in chloroform (10 mL) and treated with one drop of 35% aqueous HCl at 0°C. After 2 h at room temperature the reaction mixture was concentrated under reduced pressure and the crude product recrystallized from petroleum ether/diisopropyl ether to give pure spirocyclic **15b** (702 mg, 89% yield). mp = 66-68°C. $[\alpha]_D$ = +88 (c = 2.2, $CHCl_3$).

IR ($CHCl_3$) : 3 000, 2 965, 2 940, 1 720, 1 495, 1 460, 1 380, 1 360, 1 310, 1 260, 1 175, 1 175-1 005, 980, 950.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.78, 0.80, 0.98 (3d, J = 6.5 Hz, J = 7.0 Hz, J = 6.5 Hz, 9H, $2CH_3$-26, CH_3-24), 1.56, (m, 4H), 1.73-2.03 (m, 4H), 2.18 (dd, J = 14.0, 1.0 Hz, 1H, Ha-18), 2.34 (ddd, J = 14.0, 3.0, 1.5 Hz, 1H, Hb-18), 2.35 (s, 3H, CH_3 arom), 2.40 (m, 2H), 3.05 (dt, J = 13.0, 7.5 Hz, 1H, Ha-15), 3.18 (m, 2H, Hb-15 + H-25), 4.12 (ddt, J = 11.0, 9.5, 3.25 Hz, 1H, H-17), 7.17 (d, J = 8.0 Hz, 2H arom), 7.32 (d, J = 8.0 Hz, 2H arom).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 13.97 (CH_3-26), 17.25 (CH_3-26), 20.13 (CH_3-24), 20.93 (CH_3 arom), 28.10 (C-23), 28.26 (C-26), 30.21 (C-15) 30.98 (C-24), 35.29 (C-16), 35.49 (C-22), 46.72 (C-18), 51.78 (C-20), 66.58 (C-17), 78.98 (C-25), 98.86 (C-21), 129.69, 129.90 (2C), 132.22 (2C), 136.16, 205.72 (C-19).

MS (IC, NH_3) : m/z 394 (MH^+ 17), 377 (MH^+).

Anal calc for $C_{22}H_{32}O_3S$, 376.55 : C, 70.17, H, 8.57. Found : C, 70.06, H, 8.56.

• *(2R,6S,8R,9S) 8-Isopropyl-9-methyl-2-[2-(*p*-toluenesulfonyl)ethyl]-1,7-dioxaspiro[5.5]undecan-4-one* **15c**

■ Via *oxidation of sulfide* **15b**

To a solution of sulfide **15b** (720 mg, 1.9 mmol) in 10 mL dichloromethane was added at 0°C *m*-chloroperbenzoic acid (980 mg, 2.5 equiv). After stirring for 1 h at 20°C, the reaction mixture was diluted with water and extracted with dichloromethane (×3). Washing with saturated aqueous $NaHCO_3$ and brine followed by evaporation of the solvent and crystallization afforded the expected sulfone **15c** (629 mg, 81% yield). mp = 134-136°C (petroleum ether/diisopropyl ether). $[\alpha]_D$ = +48 (c = 2.05, $CHCl_3$).

IR ($CHCl_3$) : 3 040, 2 975, 2 940, 2 880, 1 730, 1 600, 1 460, 1 380, 1 360, 1 320, 1 310, 1 150.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.78, 0.81, 0.87 (3d, J = 7.0 Hz, 9H, $2CH_3$-26, CH_3-24), 1.40-1.98 (m, 8H), 2.12 (dd, J = 14.0, 11.0 Hz, 1H, Ha-18), 2.31 (d, J = 14.5 Hz, 1H, Ha-20), 2.32 (ddd, J = 14.0, 3.0, 1.5 Hz, 1H, Hb-18), 2.39 (dd, J = 14.5, 1.5 Hz, 1H, Hb-20), 2.47 (s, 3H, CH_3 arom), 2.93 (d wide, J = 7.0 Hz, 1H, H-25), 3.13 (ddd, J = 16.0, 7.5, 6.5 Hz, 1H, Ha-15), 3.40 (ddd, J = 16.0, 7.5, 6.5 Hz, 1H, Hb-15), 3.91 (m, 1H, H-17), 7.39 (d, J = 8.0 Hz, 2H arom), 7.81 (d, J = 8.0 Hz, 2H arom).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 13.78 (CH_3-26), 17.17 (CH_3-26), 20.25 (CH_3-24), 21.54 (CH_3 arom), 28.03 (C-23), 28.07 (C-26), 29.37 (C-16) 30.92 (C-24), 34.98 (C-22), 46.31 (C-18), 51.55 (C-20), 52.70 (C-15), 66.54 (C-17), 79.37 (C-25), 98.96 (C-21), 127.98, 129.93 (2C), 135.80 (2C), 144.79, 204.84 (C-19).

MS (EI) : m/z 408 (M^+), 390 (M-18), 336, 153, 139, 111.

Anal calc for $C_{22}H_{32}O_5S$, 408.55 : C, 64.68, H, 7.89. Found : C, 64.49, H, 7.82.

■ Via *acid-catalyzed cyclization of* **14** *(17R,S, Z = Ts, R= Me)*

The crude mixture of aldol isomers **14**-(17*RS*, Z=Ts, R=Me) (2.17 g, 4.9 mmol) was dissolved in chloroform (20 mL) and treated with two drops of 35% aqueous HCl at 0°C. After 2 h at room temperature, the reaction mixture was concentrated under reduced pressure and the residue submitted to MPLC separation (diethyl ether/pentane from 40:60 to 70:30). In order of elution, were obtained the spiroketals **15c** (see above) together with a minor amount of **17** (776 mg as a 75:25 mixture) and **16** (477 mg), corresponding to respective yields of 46, 16 and 38%.

(2*S*,6*S*,8*R*,9*S*) 8-Isopropyl-9-methyl-2-[2-(*p*-toluenesulfonyl)ethyl]-1,7-dioxaspiro-[5.5]undecan-4-one **16** : mp = 122-124°C (diisopropyl ether/hexane).

IR ($CHCl_3$) : 3 035, 2 965, 2 880, 1 730, 1 600, 1 460, 1 400, 1 390, 1 370, 1 320, 1 310, 1 290, 1 220, 1 150, 1 090, 1 010, 980.

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.74, 0.76, 0.79 (3d, J = 7.0 Hz, 9H, $2CH_3$-26, CH_3-24), 1.39-1.97 (m, 8H), 2.27 (dd, J = 16.5, 3.0 Hz, 1H, Ha-18), 2.46 (s, 3H, CH_3 arom), 2.48 (2d, J = 16.5 Hz, 2H, H-20), 2.55 (dd, J = 16.5, 12.0 Hz, 1H, Ha-18), 3.15 (m, 1H, H-25), 3.21 (ddd, J = 14.0, 11.0, 5.5 Hz, 1H, Ha-15), 3.42 (ddd, J = 14.0, 11.0, 5.0 Hz, 1H, Hb-15), 4.03 (ddt, J = 12.0, 9.0, 3.0 Hz, 1H, H-17), 7.38 (d, J = 8.0 Hz, 2H, H arom), 781 (d, J = 8.0 Hz, 2H, H arom).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 13.89 (CH_3-26), 16.86 (CH_3-26), 20.26 (CH_3-24), 21.20 (CH_3 arom), 27.40 (C-23), 27.81 (C-26), 30.14 (C-16), 30.94 (C-24), 34.48 (C-16), 43.77 (C-22), 49.63 (C-18), 52.17 (C-20), 68.36 (C-17), 79.03 (C-25), 97.64 (C-21), 127.69, 129.83 (2C), 135.48 (2C), 144.39, 205.37 (C-19).

MS (EI) : m/z 408 (M^+), 336, 297, 139, 111.

Anal calc for $C_{22}H_{32}O_5S$, 408.55 : C, 64.68, H, 7.89. Found : C, 64.75, H, 7.94.

(2*S*,6*R*,8*R*,9*S*) 8-Isopropyl-9-methyl-2-[2-(*p*-toluenesulfonyl)ethyl]-1,7-dioxaspiro-[5.5]undecan-4-one **17** :

^1H NMR ($CDCl_3$, 250 MHz), δ (deduced from the spectrum of pure **15c**) : 0.74, 0.76, 0.79 (3d, J = 7.0 Hz, 9H, $2CH_3$-26, CH_3-24), 1.4-2.3 (m, 12H), 2.46 (s, 3H, CH_3 arom), 2.95 (m, 1H, H-25), 3.21 (m, 1H, Ha-15), 3.40 (m, 1H, Hb-15), 4.33 (m, 1H, H-17), 7.38 (d, J = 8.0 Hz, 2H, H arom), 7.81 (d, J = 8.0 Hz, 2H, H arom).

• *(2*R*,4*S*,6*S*,8*R*,9*S*) 8-Isopropyl-9-methyl-2-[2-(*p*-toluenesulfonyl)ethyl]-1,7-dioxaspiro [5.5]undecan-4-ol* **18**

Pure sulfonylketone **15c** (0.9 g, 2.2 mmol) was dissolved in a 1:1 mixture (v/v) of anhydrous benzene and petroleum ether (50 mL) and treated with $LiAlH_4$ (420 mg, 5 equiv). The heterogeneous reaction mixture was stirred 1 h at 75°C and, after cooling to 0°C, successively carefully treated with water (1.65 mL), aqueous 1 N NaOH (1.65 mL), and water (4.4 mL). The solid aluminates were eliminated by filtration of the resulting mixture through a pad of celite and washed with CH_2Cl_2. The combined organic filtrates were concentrated under reduced pressure and submitted to MPLC separation. Elution with pentane/ether (fractions from 60:40 to 20:80) afforded pure **18** (643 mg, 71% yield) as well as the epimeric alcohol **19** (157 mg, 17% yield, 80:20 ratio). mp = 141-142°C (diisopropyl ether). $[\alpha]_D$ = +48 (c = 2.0, $CHCl_3$).

IR ($CHCl_3$) : 3 605-3 450, 3 040, 3 010, 2 980, 2 940, 2 880, 1 600, 1 460, 1 460, 1 380, 1 370, 1 320, 1 310, 1 290, 1 150, 1 090, 1 010, 985, 950, 865.

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.75 (d, J = 7.0 Hz, 3H, CH_3), 0.77 (d, J = 7.0 Hz, 3H, CH_3), 0.88 (d, J = 7.0 Hz, 3H, CH_3), 1.04 (q, J = 11.5 Hz, 1H, Ha-18), 1.16 (dd, J = 11.5, 11.5, 1H, Ha-20), 1.40 (m, 5H), 1.70-1.87 (m, 4H), 1.92 (ddd, J = 11.5, 4.5, 1.2 Hz, 1H, Hb-20), 2.44 (s, 3H, CH_3 arom), 2.86 (d wide, J = 6.5 Hz, 1H, H-25), 3.06 (ddd, J = 14.0, 11.0, 4.7 Hz, 1H, Ha-15), 3.34 (ddd, J = 14.0, 11.0, 5.0 Hz, 1H, Hb-15), 3.55 (dddd, J = 11.5, 8.5, 3.0, 2.0 Hz, 1H, H-17), 4.04 (tt, J = 11.5, 4.5 Hz, 1H, H-19), 7.35 (d, J = 8.0 Hz, 2H, H arom), 7.76 (d, J = 8.0 Hz, 2H, H arom).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 13.93 (CH_3-26), 17.26 (CH_3-26), 20.87 (CH_3-24), 21.51 (CH_3 arom) , 28.04 (C-23), 28.08 (C-26), 29.14 (C-16), 31.42 (C-24), 35.43 (C-22), 40.49 (C-18), 44.71 (C-20), 53.08 (C-15), 64.24 (C-17), 65.80 (C-19), 78.35 (C-25), 97.17 (C-21), 127.96, 129.84 (2C), 135.71 (2C), 144.61.

MS (EI) : m/z 410 (M^+), 393 (M-17), 320, 278, 157, 139, 122, 95.

Anal calc for $C_{22}H_{34}O_5S$, 410.56 : C, 64.36, H, 8.35. Found : C, 64.32, H, 8.24.

• *(2*R*,4*R*,6*S*,8*R*,9*S*) 8-Isopropyl-9-methyl-2-[2-(*p*-toluenesulfonyl)ethyl]-1,7-dioxaspiro [5.5]undecan-4-ol* **19**

Sulfonylketone **15c** (41 mg, 0.1 mmol) in a 2:1 (v/v) mixture of benzene/hexane (3 mL) was treated at 0°C under N_2 with 1 M L-selectride in THF (0.25 mL, 2.5 equiv). After 1 h at 0°C the reaction mixture was poured into water and extracted with ethyl acetate. Usual work-up and flash chromatography afforded the non-natural 4*R* alcohol **19** (35 mg, 86% yield) as the only detectable isomer. mp = 129-131°C ($(iPr)_2O$). $[\alpha]_D$ = +45 (c = 2.05, $CHCl_3$).

IR ($CHCl_3$) : 3 030, 3 005, 2 980, 2 960, 2 880, 1 600, 1 460, 1 440, 1 390, 1 320, 1 310, 1 260, 1 215, 1 170, 1 145, 1 090, 1 050, 1 005, 980, 870, 820.

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.81, 0.83, 0.98 (3d, J = 7.0 Hz, 9H, $2CH_3$-26 , CH_3-24), 1.34 (ddd, J = 14.0, 12.0, 2.5 Hz, 1H, Ha-18), 1.47-1.62 (m, 6H), 1.71 (dddd, J = 14.0, 3.0, 2.5, 2.0 Hz, 1H, Hb-18), 1.82 (m, 2H, CH_2-16), 1.83 (ddd, J = 14.0, 2.2, 2.0 Hz, 1H, Ha-20), 1.93 (sept d, J = 7.0, 2.0 Hz, 1H, H-26), 2.45 (s, 3H, CH_3 arom), 3.02 (m, 1H, H-25), 3.11 (ddd, J = 14.0, 10.0, 7.0 Hz, 1H, Ha-15), 3.40 (ddd, J = 14.0, 10.5, 6.0 Hz, 1H, Hb-15), 3.88 (dddd, J = 12.0, 7.0, 6.0, 2.0 Hz, 1H, H-17), 4.02 (m, 1H, H-19), 7.35 (d, J = 8.0 Hz, 2H, H arom), 780 (d, J = 8.0 Hz, 2H, H arom).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 13.93 (CH_3-26), 17.41 (CH_3-26), 21.03 (CH_3-24), 21.56 (CH_3 arom), 27.51 (C-23), 27.70 (C-26), 29.23 (C-16), 31.41 (C-24), 35.53 (C-22), 37.90 (C-18), 39.98 (C-20), 53.01 (C-15), 62.35 (C-17), 64.64 (C-19), 80.07 (C-25), 98.00 (C-21), 128.04, 129.87 (2C), 135.69 (2C), 144.61.

MS (EI) : m/z 410 (M^+), 393 (M-17), 338, 296, 157, 151, 139, 122, 55.

Anal calc for $C_{22}H_{34}O_5S$, 410.56 : C, 64.36, H, 8.35. Found : C, 64.55, H, 8.27.

*Large scale synthesis : resolution of sulfone (±)-***18**

• *(2*R**,4*S**,6*S**,8*R**,9*S**) 8-Isopropyl-9-methyl-2-[2-(*p*-toluenesulfonyl)ethyl]-1,7-dioxaspiro [5.5]undecan-4-ol (±)-***18**

The preparation of (2,6-di-*t*-butyl)phenyl propanoate **20** was carried out according to the procedure of Heathcock [20]. In a 1 L three-necked round-bottomed flask flushed with N_2 was placed 2,6-di-*t*-butylphenol (103 g, 0.5 mol) and dry THF (500 mL). After cooling to 0°C, 400 mL of *n*-BuLi (1.5 N in hexane, 1.2 equiv) were slowly added to the solution and stirred for 30 min at 0°C. Propionyl chloride (65 mL, 0.75 mol) was then added to the mixture. After stirring for 12 h at 20°C, the solution was extracted with diethyl ether, washed with a saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated. Distillation of the crude residue led to (2,6-di-*t*-butyl)phenyl propanoate **20** (125 g, 95%) : bp = 110°C/0.5 mmHg.

^1H NMR ($CDCl_3$, 250 MHz), δ : 1.35 (s, 18H, $6CH_3$), 1.40 (t, J = 7.0 Hz, 3H, CH_3), 2.60 (q, J = 7.0 Hz, 2H, CH_2), 7.10 (m, 3H, H arom).

To a cooled (−78°C) solution of LDA (0.48 mol, 1.05 equiv) was added dropwise a solution of (2,6-di-*t*-butyl)phenyl propanoate **20** (120 g, 0.48 mol, 1.05 equiv) in THF (200 mL). After stirring for 45 min at −78°C, a solution of isobutyraldehyde (42 mL, 0.46 mol, 1 equiv), in THF (100 mL) was added. After 10 min, the mixture was

diluted (−78°C) with a saturated aqueous NH_4Cl solution and the temperature was allowed to reach 20°C. The reaction mixture was extracted with diethyl ether, washed (water), dried ($MgSO_4$), and the solvent removed under reduced pressure to give (2,6-di-*t*-butyl)phenyl 3-hydroxy-2,4-dimethylpentanoate **21** which was crystallized from isooctane (124.4 g, 80%) : mp = 90°C.

IR ($CHCl_3$) : 1 760, 1 580, 1 460, 1 415, 1 385 1 350.

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.96 and 1.07 (2d, J = 7.0 Hz, 6H, CH_3-4 + H_3-5), 1.34 (d, J = 4.0 Hz, 18H, $6CH_3$, $2C(CH_3)_3$), 1.48 (d, J = 7.5 Hz, 3H, CH_3-2), 1.96 (d sept J = 7.0, 4.0 Hz, 1H, H-4), 2.88 (quint, J = 7.7 Hz, 1H, H-2), 3.68 (dd, J = 7.7, 4.0 Hz, 1H, H-3), 7.17 (t, J = 8.0 Hz, 1H, H arom), 7.40 (dq, J = 8.0, 4.0 Hz, 2H, H arom).

MS (CI, NH_3) : m/z 335(MH^+).

Anal calc for $C_{21}H_{34}O_3$, 334.50 : C, 75.41, H, 10.25. Found : C, 75.59, H, 10.26.

To a cooled (0°C) suspension of $LiAlH_4$ (14.5 g, 0.38 mol, 1.05 equiv) in diethyl ether (600 mL) was slowly added a solution of the above pentanoate (123 g, 0.36 mol), in diethyl ether (400 mL). After 1 h at 0°C were successively added H_2O (40 mL), aqueous NaOH (1 N, 40 mL) and H_2O (70 mL). After 30 min at room temperature the mixture was filtered, dried ($MgSO_4$), and the solvent removed under reduced pressure to give compound (±)-**9** which was then purified by chromatography (43 g, 90.5% yield; *anti/syn* = 99:1 from GC analysis). Its spectroscopic data were fully consistent with those already reported for optically active diol (+)-**9**.

The reactions allowing transformation of (±)-**9** into the racemic hydroxysulfone (±)-**18** were carried out as previously described in the optically active series. The crucial aldolization step leading to the C15-C25 avermectin fragment was performed according to the general procedure on a 0.2 mol scale between methyl acetal (±)-**12b** with the sulfonylpropanal **6c** to give, after cyclization and reduction, the racemic hydroxysulfone (±)-**18** which was spectroscopically identical to optically active (±)-**18** prepared above.

• *Resolution of (±)-***18** *through its O-acetylmandelic ester*

The preparation of (−)-*O*-acetylmandelic acid was carried out using a slight modification of Whitesell's procedure [46]. To a solution of commercial (*R*)-(−)-mandelic acid (15.2 g, 0.1 mol) in a mixture of CH_2Cl_2 (80 mL) and pyridine (8.9 mL, 1.1 equiv) was slowly added over a 15 min period, at 0°C, acetyl chloride (7.47 mL, 1.05 equiv) diluted with 20 mL of CH_2Cl_2). After stirring for 2 h at 20°C, the reaction mixture was poured into ice-cooled water and extracted with CH_2Cl_2 (×3). The combined organic phases were carefully washed with brine, evaporated, and thoroughly dried in a dessicator to give (*R*)-(−)-*O*-acetylmandelic acid (19.9 g, quantitative) as a colorless oil, $[\alpha]_D$ = −152 (c = 3.0, acetone), Lit : $[\alpha]_D$ = −155 (c = 2.4, acetone).

To a mixture of racemic hydroxysulfone (±)-**18** (9.1 g, 22.2 mmol), (−)-*O*-acetylmandelic acid (6 g, 1.4 equiv) and 4-(dimethylamino)pyridine (270 mg, 0.1 equiv), was added at 0°C dicyclohexylcarbodiimide (6 g, 1.3 equiv) dissolved in 20 mL CH_2Cl_2. The reaction mixture was stirred overnight at room temperature, and then diluted with 0.5 N aqueous HCl (40-50 mL) and decanted. After two further extractions with CH_2Cl_2, the combined organic phases were successively washed with brine, saturated $NaHCO_3$, brine, and then dried over $MgSO_4$ and evaporated *in vacuo* to give the expected (*R*)-(−)-*O*-acetylmandelic esters (13.73 g). Two successive MPLC separations (Lichroprep Si 60 Merck Art 13905), gave in order of elution (increasing gradient from 1:9 to 3:7 of a mixture of diisopropyl ether/isopropanol 49:1 in hexane/toluene 1:1) pure [2*R*(2*R*,4*S*,6*S*,8*R*,9*S*) (8-isopropyl-9-methyl-2-[2-(p-toluenesulfonyl)ethyl]-1,7-dioxaspiro[5.5]-undecan-4-ol) 2-acetoxy-2-phenyl acetic acid ester (5.18 g, 80% yield) and [2*R*(2*S*,4*R*,6*R*,8*S*,9*R*)] (8-isopropyl-9-methyl-2-[2-(p-toluenesulfonyl)ethyl]-1,7-dioxaspiro[5.5]-undecan-4-ol) 2-acetoxy-2-phenyl acetic acid ester (5.96 g, 92% yield).

■ *[2R(2R,4S,6S,8R,9S) (8-Isopropyl-9-methyl-2-[2-(p-toluenesulfonyl)ethyl]-1,7-dioxaspiro-[5.5]undecan-4-ol) 2-acetoxy-2-phenyl acetic acid ester*

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.78 (d, J = 6.0 Hz, 3H, CH_3), 0.78 (d, J = 7.0 Hz, 3H, CH_3), 0.91 (d, J = 7.0 Hz, 3H, CH_3), 1.0-1.6 (m, 7H), 1.7-1.9 (m, 4H), 1.96 (ddd, J = 14.5, 5.5, 1.0 Hz, 1H, Hb-20), 2.18 (s, 3H, CH_3, $COCH_3$), 2.47 (s, 3H, CH_3 arom), 2.87 (d wide, J = 7.0 Hz, 1H, H-25), 3.06 (ddd, J = 14.0, 11.0, 4.75 Hz, 1H, Ha-15), 3.35 (ddd, J = 14.0, 9.0, 6.7 Hz, 1H, Hb-15), 3.6 (m, 1H, H-17), 5.14 (tt, J = 11.3, 4.9 Hz, 1H, H-19), 5.79 (s, 1H, Ph-C*H*OAc), 7.4 (m, 7H, H arom), 7.77 (d, J = 8.0 Hz, 2H, H arom).

MS (IC, NH_3) : m/z 604 (MH^+ + NH_3), 587 (MH^+), 393, 375, 349, 337, 321, 295, 278, 237, 212, 139, 122, 108.

■ *[2R(2S,4R,6R,8S,9R)] (8-Isopropyl-9-methyl-2-[2-(p-toluenesulfonyl)ethyl]-1,7-dioxaspiro [5.5]undecan-4-ol) 2-acetoxy-2-phenyl acetic acid ester*

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.77 (d, J = 6.0 Hz, 3H, CH_3), 0.78 (d, J = 7.0 Hz, 3H, CH_3), 0.89 (d, J = 7.0 Hz, 3H, CH_3), 1.0-1.6 (m, 7H), 1.7-1.9 (m, 4H), 2.03 (ddd, J = 14.5, 5.5, 1.0 Hz, 1H, Hb-20), 2.19 (s, 3H, CH_3, $COCH_3$), 2.46 (s, 3H, CH_3 arom), 2.88 (d wide, J = 7.0 Hz, 1H, H-25), 3.03 (ddd, J = 14.0, 11.0, 4.75 Hz, 1H, Ha-15), 3.32 (ddd, J = 14.0, 9.0, 6.7 Hz, 1H, Hb-15), 3.58 (m, 1H, H-17), 5.16 (tt, J = 11.3, 4.9 Hz, 1H, H-19), 5.82 (s, 1H, Ph-C*H*OAc), 7.4 (m, 7H, H arom), 7.76 (d, J = 8.0 Hz, 2H, H arom).

MS (IC, NH_3) : m/z 604 (MH^+ + NH_3), 587 (MH^+), 393, 375, 349, 337, 139, 122, 108.

Each aforementioned isomeric batch has been separately treated with 1.5 M methanolic potassium carbonate (0.1 mmol/50 mL) solution for 2 h at room temperature. The reaction mixture was diluted with water, saturated with sodium chloride and extracted with diethyl ether (×3) to give, after drying the combined organic phases over $MgSO_4$, evaporation and crystallization from diisopropylether/isooctane, the expected hydroxysulfone, (+)-**18** (3.1 g, 84% yield; $[\alpha]_D$ = +48; (c = 2.0, $CHCl_3$; 100% ee) Cf above) or (−)-*ent*-**18** (3.3 g, 79% yield; $[\alpha]_D$ = −43; (c = 2.0, $CHCl_3$; 92% ee) respectively.

■ *(2S,4R,6R,8S,9R) 8-Isopropyl-9-methyl-2-[2-(p-toluenesulfonyl)ethyl]-1,7-dioxaspiro [5.5]undecan-4-ol* ent-**18**

All spectroscopic data obtained for (−)-*ent*-**18** were identical to those of (+)-**18**.

Synthesis of the C10-C25 North fragment of dihydroavermectin B1b **1**

• *[2E(2R,4S,6S,8R,9S)] 4-{8-Isopropyl-9-methyl-4-[(trimethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecan-2-yl}-2-methylbut-2-enal* **25**

To a solution of (+)-**18** (2.05 g, 5 mmol) in dichloromethane (10 mL) were added pyridine (0.6 mL) and TMSCl (0.8 mL,

6.3 mmol, 1.25 equiv). After stirring overnight at room temperature the reaction mixture was partially evaporated, diluted with hexane containing a few drops of Et_3N and poured over a short column of $NaHCO_3$-treated silica gel. Elution with hexane/diethyl ether (fractions from 1:0 to 0:1) afforded the pure expected silyl ether **22** in quantitative yield (2.44 g).

■ *(2R,4S,6S,8R,9S) 8-Isopropyl-9-methyl-2-[2-(p-toluenesulfonyl)ethyl]-4-[(trimethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecane* **22**

^{1}H NMR ($CDCl_3$, 250 MHz), δ : −0.1 (s, 9H, $3CH_3$, $Si(CH_3)_3$), 0.69 (d, J = 7.0 Hz, 3H, CH_3), 0.73 (d, J = 7.0 Hz, 3H, CH_3), 0.84 (d, J = 7.0 Hz, 3H, CH_3), 0.9-1.9 (m, 12H), 2.37 (s, 3H, CH_3 arom), 2.77 (d wide, J = 7.0 Hz, 1H, H-25), 2.97 (ddd, J = 14.0, 11.0, 4.75 Hz, 1H, Ha-15), 3.24 (ddd, J = 14.0, 11.0, 5.0 Hz, 1H, Hb-15), 3.46 (dddd, J = 11.5, 8.5, 3.0, 2.0 Hz, 1H, H-17), 3.95 (tt, J = 11.5, 4.5 Hz, 1H, H-19), 7.28 (d, J = 8.0 Hz, 2H, H arom), 7.70 (d, J = 8.0 Hz, 2H, H arom).

The preceding sulfonyl trimethylsilyl ether **22** (2.40 g) in THF (20 mL) was treated at −78°C under nitrogen with an LDA stock solution (1.06 M, 5.2 mL, 1.1 equiv). After stirring for 5 min at −78°C, and then for 30 min at 0°C, the reaction mixture was cooled again at −78°C and successively treated with HMPA (0.92 mL, 1.05 equiv), and, after 5 min, with 2-bromopent-3-ene [21]. After further stirring for 1 h at −78°C and for 1 h at 0°C, the mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether (×3). Usual work-up including evaporation of the solvent gave the crude alkylated sulfone **23** (2.70 g, quantitative).

This reaction was conducted on a second batch of 1.45 g of the above sulfonyl trimethylsilyl ether **22** to give 2.11 g of crude product **23**.

The two crude extracts were combined (4.81 g) and submitted to silica gel ($NaHCO_3$-treated) flash chromatography (elution with hexane/diethyl ether gradient from 1:0 to 0:1) to yield 4.15 g (94% yield) of pure **23** as a mixture of diastereomers.

■ *[2R(2RS,3RS,4E),4S,6S,8R,9S] 8-Isopropyl-9-methyl-2-[3-methyl-2-(p-toluenesulfonyl)hex-4-enyl]-4-[(trimethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecane* **23**

^{1}H NMR ($CDCl_3$, 250 MHz), 2 diastereoisomers, δ : −0.02, −0.01 (2s, 9H, $3CH_3$, $Si(CH_3)_3$), 0.68 (d, J = 6.0 Hz, 3H, CH_3), 0.69 (d, J = 7.0 Hz, 3H, CH_3), 0.73 (d, J = 7.0 Hz, 3H, CH_3), 0.89 (2d, J = 7.0 Hz, 3H, CH_3-14), 1.16-1.90 (m, 12H), 1.68, 1.73 (2s wide, 3H, CH_3-12), 2.31, 2.34 (2s, 3H, CH_3 arom), 2.51, 2.70 (2m, 1H), 2.78, 3.01 (2m, 1H, H-25), 3.15, 3.22 (2m, 1H, H-15), 3.52, 3.74 (2m, 1H, H-17), 3.96 (m, 1H, H-19), 5.18, 5.32 (2m, 2H, H-12 + H-13), 7.21 (2d, J = 8.0 Hz, 2H, H arom), 7.62 (2d, J = 8.0 Hz, 2H, H arom).

Ozone was gently bubbled at through a solution of the preceding olefin **23** (0.46 g, 1 mmol) in dichloromethane (30 mL) −78°C. After 10 min the blue solution was partially concentrated (10 mL) using a stream of nitrogen under a well ventilated hood (10 mL), and triethylamine (0.7 mL, 5 equiv) and dimethylaminopyridine (5 mg) were added at −78°C. The reaction mixture was allowed to warm to room temperature and, after 4 h, was diluted with hexane and chromatographed on silica gel ($NaHCO_3$-treated). Elution with pentane/diethyl ether fractions 1:0 to 0:1 afforded, in order of elution, the expected silylated aldehyde **25** (319 mg, 84% yield) as well as a small amount of the desilylated starting material **23** (21 mg, 7% yield, see below).

25 : ^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.0 (s, 9H, $3CH_3$, $Si(CH_3)_3$), 0.63 (d, J = 6.0 Hz, 3H, CH_3), 0.70 (d, J = 7.0 Hz, 3H, CH_3), 0.82 (d, J = 7.0 Hz, 3H, CH_3), 1.10-1.5 (m, 6H), 1.64 (d, J = 1.0 Hz, 3H, CH_3-14), 1.73 (m, 4H), 2.4 (t, J = 7.3 Hz, 2H, CH_2-16), 2.82 (d wide, J = 7.0 Hz, 1H, H-25), 3.60 (m, 1H, H-17), 3.99 (m, 1H, H-19), 6.94 (tq, J = 7.3, 1.0 Hz, 1H, H-15), 9.3 (s, 1H, CHO).

• *[2E(2R,4S,6S,8R,9S)] 4-{8-Isopropyl-9-methyl-4-[(triethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecan-2-yl}-2-methylbut-2-enal* **26**

Trimethylsilyl ether **23** (4.6 g) was dissolved in MeOH and stirred for 1 h at room temperature with Amberlyst-15. After filtration on Na_2CO_3, the solvent was thoroughly evaporated to give the corresponding alcohol in quantitative yield (4.03 g).

■ *[2R(2RS,3RS,4E),4S,6S,8R,9S] 4-Hydroxy-8-isopropyl-9-methyl-2-[3-methyl-2-(p-toluenesulfonyl) hex-4-en-yl]-1,7-dioxaspiro[5.5]undecane*

^{1}H NMR ($CDCl_3$, 250 MHz), 2 diastereomers δ : 0.7-0.9 (3d, J = 6.0, 7.0, 7.0 Hz, 9H, $3CH_3$), 0.89 (2d, J = 7.0 Hz, 3H, CH_3-14), 1.16-2.20 (m, 12H), 1.63, 1.65 (2s wide, 3H, CH_3-12) 2.43, 2.45 (2s, 3H, CH_3 arom), 2.50-2.80 (2m, 1H), 2.90, 3.01 (2m, 1H, H-25), 3.25, 3.35 (2m, 1H, H-15), 3.68, 3.86 (2m, 1H, H-17), 4.10 (m, 1H, H-19), 5.25, 5.40 (2m, 2H, H-12 + H-13), 7.25 (2d, J = 8.0 Hz, 2H, H arom), 7.60 (2d, J = 8.0 Hz, 2H, H arom).

The above alcohol (4.03 g) was dissolved in dichloromethane (16 mL) and treated with pyridine (1.35 mL), DMAP (5 mg) and triethylchlorosilane (2.1 mL, 1.5 equiv). After stirring for 2 h at room temperature, the reaction mixture was diluted with hexane and purified on a silica-gel column ($NaHCO_3$-treated, elution with hexane/diethyl ether) to give the corresponding triethylsilyl ether **24** in quantitative yield.

■ *[2R(2RS,3RS,4E),4S,6S,8R,9S] 8-Isopropyl-9-methyl-2-[3-methyl-2-(p-toluenesulfonyl)hex-4-enyl]-4-[(triethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecane* **24**

^{1}H NMR ($CDCl_3$, 250 MHz), 2 diastereoisomers δ : 0.59 (2q, J = 7.0 Hz, 6H, $Si(CH_2\text{-}CH_3)_3$), 0.7-0.9 (3d, J = 6.0, 7.0, 7.0 Hz, 9H, $3CH_3$), 0.89 (2d, J = 7.0 Hz, 3H, CH_3-14), 0.97 (2t, J = 7.0 Hz, 9H, $Si(CH_2\text{-}CH_3)_3$), 1.10-2.0 (m, 12H), 1.60, 1.62 (2s wide, 3H, CH_3-12), 2.40, 2.42 (2s, 3H, CH_3 arom), 2.60, 2.80 (2m, 1H), 2.86, 3.1 (2m, 1H, H-25), 3.28, 3.38 (2m, 1H, H-15), 3.61, 3.82 (2m, 1H, H-17), 4.08 (m, 1H, H-19), 5.28, 5.45 (2m, 2H, H-12′ + H-13), 7.25 (2d, J = 8.0 Hz, 2H, H arom), 7.75 (2d, J = 8.0 Hz, 2H, H arom).

MS (CI, NH_3) : m/z 593 (MH^+), 547, 496, 479, 461, 439, 415, 325, 305, 283, 247, 234, 132, 120, 102.

Ozonolysis was carried out on the above olefinic-sulfone derivative (2.23 g, 3.8 mmol), as already described, to give, after chromatography, the pure expected triethylsilyl ether aldehyde **26** (1.2 g, 75% yield).

26 : $[\alpha]_D$ = +41 (c = 2, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.52, 0.60, 0.61 (3q, J = 7.0 Hz, 6H, $Si(CH_2\text{-}CH_3)_3$), 0.76 (d, J = 7.0 Hz, 3H, CH_3), 0.82 (d, J = 7.0 Hz, 3H, CH_3), 0.93, 0.96, 0.97 (3t, J = 7.0 Hz, 9H, $Si(CH_2\text{-}CH_3)_3$), 0.94 (d, J = 7.0 Hz, 3H, CH_3), 1.33 (m, 2H), 1.48 (m, 2H), 1.63 (m, 2H), 1.77 (d, J = 1.0 Hz, 3H, CH_3-14), 1.87 (m, 4H), 2.53 (tq, J = 7.0, 1.0 Hz, 2H, CH_2-16), 2.95 (dd, J = 7.0, 2.5 Hz, 1H, H-25), 3.71 (ddt, J = 11.6, 7.0, 5.5 Hz, 1H, H-17), 4.14 (tt, J = 11.0, 4.6 Hz, 1H, H-19), 6.62 (tq, J = 7.0, 1.0 Hz, 1H, H-15), 9.43 (s, 1H, CHO).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 4.82 (3C, $Si(CH_2\text{-}CH_3)_3$), 6.69 ($3CH_3$, $Si(CH_2\text{-}CH_3)_3$), 9.26 (CH_3-14), 13.94 (CH_3-26), 17.34 (CH_3-26), 20.86 (CH_3-24), 28.05

(C-23), 28.13 (C-26), 31.38 (C-24), 35.11 (C-16), 35.47 (C-22), 41.26 (C-18), 45.32 (C-20), 65.04 (C-19), 66.75 (C-17), 78.27 (C-25), 97.3 (C-21), 140.44 (C-14), 150.69 (C-15), 194.83 (C-13, CHO).

MS (CI, NH_3) : m/z 442 ($MH^+ + NH_3$), 425 (MH^+), 352, 310, 293 (M^+ - OTES).

• *2E(2S,4R,6R,8S,9R)] 4-{8-Isopropyl-9-methyl-4-[(trimethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecan-2-yl}-2-methylbut-2-enal* ent-**25**
[2E(2S,4R,6R,8S,9R)] 4-{8-Isopropyl-9-methyl-4-[(triethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecan-2-yl}-2-methylbut-2-enal ent-**26**

The enantiomeric triethylsilylether aldehydes *ent*-**25** and *ent*-**26** were prepared in the same way as **25** and **26** starting from (−)-*ent*-**18**. All intermediates were shown to be consistent with those obtained in the natural series.

ent-**26** : ^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.60 (q, J = 7.5 Hz, 6H, Si(CH_2-CH_3)$_3$), 0.76 (d, J = 7.0 Hz, 3H, CH_3), 0.81 (d, J = 7.0 Hz, 3H, CH_3), 0.93 (d, J = 7.0 Hz, 3H, CH_3), 0.93 (t, J = 7.5 Hz, 9H, Si(CH_2-CH_3)$_3$), 1.33 (m, 2H), 1.48 (m, 2H), 1.63 (m, 2H), 1.77 (d, J = 1.0 Hz, 3H, CH_3-14), 1.87 (m, 4H), 2.53 (tq, J = 7.0, 1.0 Hz, 2H, CH_2-16), 2.95 (dd, J = 7.0, 2.5 Hz, 1H, H-25), 3.71 (ddt, J = 11.5, 7.0, 5.5 Hz, 1H, H-17), 4.14 (tt, J = 11.0, 4.6 Hz, 1H, H-19), 6.62 (tq, J = 7.0, 1.0 Hz, 1H, H-15), 9.43 (s, 1H, CHO).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 4.82 (3C, 3Si-CH_2-CH_3), 6.69 (3CH_3, 3Si-CH_2-CH_3), 9.26 (CH_3-14), 13.94 (CH_3-26), 17.34 (CH_3-26), 20.86 (CH_3-24), 28.05 (C-23), 28.13 (C-26), 31.38 (C-24), 35.11 (C-16), 35.47 (C-22), 41.26 (CH_2-18), 45.32 (C-20), 65.04 (C-19), 66.75 (C-17), 78.27 (C-25), 97.3 (C-21), 140.44 (C-14), 150.69 (C-15), 194.83 (C-13, CHO).

• *Homoaldolization according to D Hoppe [10]*
[2R(2E,6Z,4S,5S),4S,6S,8R,9S)] 2-{7-[(N,N-Diisopropylcarbamoyl)oxy]-3,5-dimethyl-4[(triisopropylsilyl)oxy]hepta-2,6-dienyl}-8-isopropyl-9-methyl-4-[(triethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecane **27**
[2R(2E,6Z,4R,5R),4S,6S,8R,9S] 2-{7-[(N,N-Diisopropylcarbamoyl)oxy]-3,5-dimethyl-4[(triisopropylsilyl)oxy]hepta-2,6-dienyl}-8-isopropyl-9-methyl-4-[(triethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecane **28**

A solution of *sec*-butyllithium (1.1 M, 6.5 mmol, 1 equiv, in cyclohexane/isopentane) was added to a solution of distilled (−)-sparteine (115°C/0.01 mmHg, 1.52 g, 6.55 mmol) in a mixture of pentane (20 mL) and cyclohexane (3.5 mL) at −78°C. After 10 min, a solution of the (*E*)-but-2-enyl *N,N*-diisopropylcarbamate (95-100°C/6-12 mmHg, 1.4 g, 7 mmol, 1.1 equiv) in pentane (5 mL) was slowly added to the stirred suspension. After about 10 min a thick white precipitate was obtained which was brought into suspension by shaking the flask. After a further 30 min magnetic stirring, Ti(^{i}PrO)$_4$ (7.65 mL, 25.7 mmol, 4 equiv) was added by cannula while the solution turned orange-red. After another 30 min at −78°C, the aldehyde **26** (1.7 g, 4 mmol, 0.6 equiv) in pentane (4.5 mL) was slowly added *via* a syringe and the reaction mixture was stirred 2 h at −78°C. It then allowed to warm to 0°C and diluted with diethyl ether and aqueous saturated NH_4Cl. After extraction with diethyl ether (3×), the combined organic phases were washed with water (3×), brine (3×), dried over $MgSO_4$ and the solvent was removed under vacuum. The crude residue was purified by chromatography on silica gel to gave in order of elution the major 4*S*,5*S*-aldol isomer (colorless oil, 1.9 g, 76%) and its minor 4*R*,5*R*-isomer (360 mg, 12%) corresponding to a 4*S*,5*S*/4*R*,5*R* ratio of 84:16.

■ *[2R(2E,6Z,4S,5S),4S,6S,8R,9S)] 2-{7-[(N,N-Diisopropylcarbamoyl)oxy]-4-hydroxy-3,5-dimethylhepta-2,6-dienyl}-8-isopropyl-9-methyl-4-[(triethylsilyl)oxy]-1,7-dioxaspiro-[5.5]undecane (major compound)*

$[\alpha]_D$ = +19.7 (c = 1.4, $CHCl_3$).

IR ($CHCl_3$) : 3 500-3 400, 1 690, 1 670, 1 520, 1 470, 1 430, 1 300, 1 200.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.57 (q, J = 8.0 Hz, 6H, Si(CH_2-CH_3)$_3$), 0.77 (d, J = 7.0 Hz, 3H, CH_3-26), 0.81 (d, J = 7.0 Hz, 3H, CH_3-26), 0.85 (d, J = 7.0 Hz, 3H, CH_3-12), 0.88 (d, J = 7.0 Hz, 3H, CH_3-24), 0.94 (t, J = 8.0 Hz, 9H, Si(CH_2-CH_3)$_3$), 1.26 (m, 12H, 4CH_3, 2N-CH(CH_3)$_2$), 1.40-1.55 (m, 6H, CH_2-22 + CH_2-23 + H-24 + H-26), 1.64 (d, J = 1.0 Hz, 3H, CH_3-14), 1.8-1.9 (m, 4H, CH_2-18 + CH_2-20), 2.18 (ddd, J = 12.5, 7.5, 6.5 Hz, 1H, Ha-16), 2.28 (ddd, J = 12.5, 7.0, 6.5 Hz, 1H, Hb-16), 2.88 (m, 1H, H-12), 3.04 (dd, J = 10.0, 2.5 Hz, 1H, H-25), 3.58 (m, 1H, H-17), 3.64 (d, J = 8.8 Hz, 1H, H-13), 3.70 (m, 1H, N-CH(CH_3)$_2$), 4.10 (m, 1H, N-CH(CH_3)$_2$), 4.10 (m, 1H, H-19), 4.64 (dd, J = 10.0, 6.5 Hz, 1H, H-11), 5.47 (tq, J = 7.0, 1.0 Hz, 1H, H-15), 7.16 (d, J = 6.5 Hz, 1H, H-10).

^{13}C NMR ($CDCl_3$, 100.57 MHz), (*H-COR correlation*) δ : 5.05 (3C, Si-CH_2-CH_3), 6.90 (3CH_3, Si-CH_2-CH_3), 11.13 (CH_3-14), 14.19 (CH_3-26), 17.49 (CH_3-26), 17.72 (CH_3-12), 20.49 (2CH_3, N-CH(CH_3)$_2$), 20.97 (CH_3-24), 21.62 (2CH_3, N-CH(CH_3)$_2$), 28.27 (C-23), 28.37 (C-26), 31.77 (C-24), 34.32 (C-16), 34.61 (C-12), 35.86 (C-22), 41.50 (C-18), 45.76 (C-20), 45.76 (N-CH(CH_3)$_2$), 47.03 (N-CH(CH_3)$_2$), 65.53 (C-19), 68.03 (C-17), 78.09 (C-25), 82.25 (C-13), 97.4 (C-21), 113.44 (C-11), 125.62 (C-15), 136.44 (C-14), 137.17 (C-10), 152.95 (CO).

MS : (CI, NH_3) : m/z 641 ($MH^+ + NH_3$), 624 (MH^+), 606 (MH^+ - 18), 594 (M^+ - 29), 492 (M^+ - OTES), 479 (M^+ - OTES - 18), 442 (M^+ - 198 + 17), 425 (M^+ - 198), 341, 293 (M^+ - 198 - HOTES), 216 (199 + NH_3), 199, 128.

Anal calc for $C_{35}H_{65}O_6NSi$, 623.94 : C, 67.37, H, 10.50, N, 2.24. Found : C, 67.43, H, 10.40, N, 2.24.

■ *[2R(2E,6Z,4R,5R),4S,6S,8R,9S] 2-{7-[(N,N-Diisopropylcarbamoyl)oxy]-4-hydroxy-3,5-dimethylhepta-2,6-dienyl}-8-isopropyl-9-methyl-4-[(triethylsilyl)oxy]-1,7-dioxaspiro-[5.5]undecane (minor compound)*

IR ($CHCl_3$) : 3 500-3 400, 1 690, 1 670, 1 520, 1 470, 1 430, 1 300, 1 200.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.52 (q, J = 8.0 Hz, 6H, Si(CH_2-CH_3)$_3$), 0.72 (d, J = 7.0 Hz, 3H, CH_3-12), 0.77 (d, J = 7.0 Hz, 3H, CH_3-26), 0.81 (d, J = 7.0 Hz, 3H, CH_3-26), 0.87 (d, J = 7.0 Hz, 3H, CH_3-24), 0.89 (t, J = 8.0 Hz, 9H, Si(CH_2-CH_3)$_3$), 1.19 (m, 12H, 2N-CH(CH_3)$_2$), 1.4-1.63 (m, 6H, CH_2-22 + CH_2-23 + H-24 + H-26), 1.58 (d, J = 1.0 Hz, 3H, CH_3-14), 1.7-1.8 (m, 4H, CH_2-18 + CH_2-20), 2.19 (t, J = 6.9 Hz, 2H, CH_2-16), 2.84 (m, 1H, H-12), 2.97 (dd, J = 9.5, 2.5 Hz, 1H, H-25), 3.50 (m, 1H, H-17), 3.58 (d, J = 9.6 Hz, 1H, H-13), 3.75 (m, 1H, N-CH(CH_3)$_2$), 4.04 (m, 1H, N-CH(CH_3)$_2$), 4.04 (m, 1H, H-19), 4.57 (dd, J = 9.9, 6.4 Hz, 1H, H-11), 5.43 (tq, J = 7.0, 1.0 Hz, 1H, H-15), 7.12 (dd, J = 5.9, 0.6 Hz, 1H, H-10).

MS (CI, NH_3) : m/z 641 ($MH^+ + NH_3$), 624 (MH^+), 606 (MH^+ - 18), 594, 492 (M^+ - OTES), 479, 442, 425, 341, 293, 199, 216, 128.

Triisopropylsilyl triflate (TIPSOTf, 1.1 mL, 1.5 equiv) was added to a cooled (0°C) solution of the above major

isomer (1.64 g, 2.63 mmol) in a mixture of CH_2Cl_2 (7 mL) and 2,6-lutidine (0.9 mL, 3 equiv). After 10 min at 0°C and 20 min at 20°C the reaction mixture was extracted with diethyl ether (3×) and the organic phases were washed with water (3×), brine (3×), dried over $MgSO_4$ and the solvent removed under vacuum. The crude residue was purified by chromatography on silica gel to afford pure title compound **27** (1.92 g, 93%).

27 : $[\alpha]_D = +32.7$ ($c = 1.05$, $CHCl_3$).

IR ($CHCl_3$) : 1 680, 1 650, 1 510, 1 460, 1 430, 1 200, 1 050.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.52 (q, J = 8.0 Hz, 6H, Si(CH_2-CH_3)$_3$), 0.71 (d, J = 7.0 Hz, 3H, CH_3-24), 0.75 (d, J = 7.0 Hz, 3H, CH_3-26), 0.80 (d, J = 7.0 Hz, 3H, CH_3-26), 0.89 (t, J = 8.0 Hz, 9H, Si(CH_2-CH_3)$_3$), 0.95 (d, J = 7.0 Hz, 3H, CH_3-12), 0.95 (s wide, 9H, 2CH_3, Si-CH(CH_3)$_2$), 0.98-1.05 (s wide, 15H, 3CH + 4CH_3, 3Si-CH(CH_3)$_2$ + 2Si-CH(CH_3)$_2$), 1.17 (m, 12H, 2N-CH(CH_3)$_2$), 1.40-1.60 (m, 6H, CH_2-22 + CH_2-23 + H-24 + H-26), 1.54 (d, J = 1.0 Hz, 3H, CH_3-14), 1.70-1.80 (m, 4H, CH_2-18 + CH_2-20), 2.12 (t, J = 7.0 Hz, 2H, CH_2-16), 2.82 (m, 1H, H-12), 2.98 (dd, J = 9.7, 2.5 Hz, 1H, H-25), 3.49 (m, 1H, H-17), 3.69 (m, 1H, N-CH(CH_3)$_2$), 3.84 (d, J = 7.3 Hz, 1H, H-13), 4.04 (m, 1H, N-CH(CH_3)$_2$), 4.04 (m, 1H, H-19), 4.57 (dd, J = 9.8, 6.5 Hz, 1H, H-11), 5.29 (tq, J = 7.0, 1.0 Hz, 1H, H-15), 6.95 (dd, J = 6.5, 0.6 Hz, 1H, H-10).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 4.92 (3C, Si-CH_2-CH_3), 6.69 (3CH_3, Si-CH_2-CH_3), 12.08 (CH_3-14), 12.27 (2C, Si-CH(CH_3)$_2$), 12.61 (Si-CH(CH_3)$_2$), 14.06 (CH_3-26), 17.31 (CH_3-26), 17.67 (4CH_3, Si-CH(CH_3)$_2$), 17.81 (CH_3-12), 18.13 (Si-CH(CH_3)$_2$), 18.17 (Si-CH(CH_3)$_2$), 20.36 (2CH_3, N-CH(CH_3)$_2$), 20.75 (CH_3-24), 21.48 (2CH_3, N-CH(CH_3)$_2$), 28.13 (C-23), 28.27 (C-26), 31.67 (C-24), 34.19 (C-16), 35.69 (C-12), 35.73 (C-22), 41.39 (CH_2-18), 45.84 (C-20), 45.85 (N-CH(CH_3)$_2$), 47.00 (N-CH(CH_3)$_2$), 65.38 (C-19), 67.76 (C-17), 77.94 (C-25), 82.58 (C-13), 97.28 (C-21), 114.49 (C-11), 123.64 (C-15), 134.82 (C-10), 137.88 (C-14), 152.95 (CO).

MS (CI, NH_3) : m/z 797 (MH^+ + NH_3), 780 (MH^+), 750, 736 (M^+ - 43), 606 (M^+ - HOTIPS), 581 (M^+ - 198), 474 (M^+ - OTES - HOTIPS), 449 (M^+ - 199 - HOTES), 341, 323, 293, 199, 128.

Anal calc for $C_{44}H_{85}O_6NSi_2$, 780.25 : C, 67.72, H, 10.98, N, 1.79. Found : C, 67.57, H, 11.04, N, 1.77.

The minor homoaldolization product (285 mg, 0.46 mmol) was silylated in the same manner using TIPSOTf (0.2 mL, 1.5 equiv) in CH_2Cl_2 (3 mL) and 2,6-lutidine (0.2 mL, 3 equiv) to give **28** (250 mg) in 70% yield.

28 : $[\alpha]_D = +19.3$ ($c = 0.95$, $CHCl_3$).

IR ($CHCl_3$) : 1 680, 1 650, 1 510, 1 460, 1 430, 1 200, 1 050.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.52 (q, J = 8.0 Hz, 6H, Si(CH_2-CH_3)$_3$), 0.72 (d, J = 6.0 Hz, 3H, CH_3), 0.75 (d, J = 6.8 Hz, 3H, CH_3), 0.80 (d, J = 6.8 Hz, 3H, CH_3), 0.89 (t, J = 8.0 Hz, 9H, Si(CH_2-CH_3)$_3$), 0.95-1.08 (s wide, 21H, 3CH + 6CH_3, 3Si-CH(CH_3)$_2$), 0.96 (d, J = 7.0 Hz, 3H, CH_3-12), 1.18 (m, 12H, 2N-CH(CH_3)$_2$), 1.40-1.60 (m, 6H, CH_2-22 + CH_2-23 + H-24 + H-26), 1.53 (d, J = 1.0 Hz, 3H, CH_3-14), 1.70-1.80 (m, 4H, CH_2-18 + CH_2-20), 2.14 (m, 2H, CH_2-16), 2.84 (m, 1H, H-12), 2.98 (dd, J = 7.8, 1.5 Hz, 1H, H-25), 3.48 (m, 1H, H-17), 3.72 (m, 1H, N-CH(CH_3)$_2$), 3.84 (d, J = 7.7 Hz, 1H, H-13), 4.04 (m, 1H, N-CH(CH_3)$_2$), 4.04 (m, 1H, H-19), 4.58 (dd, J = 9.9, 6.6 Hz, 1H, H-11), 5.31 (tq, J = 7.0, 1.0 Hz, 1H, H-15), 6.97 (dd, J = 6.6, 0.6 Hz, 1H, H-10).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 4.88 (3C, 3Si-CH_2-CH_3), 6.8 (3CH_3, 3Si-CH_2-CH_3), 11.92 (CH_3-14), 12.57 (3C, 3Si-CH(CH_3)$_2$), 14.06 (CH_3-26), 17.34 (CH_3-12), 17.58 (CH_3-26), 18.12 (3CH_3, 3Si-CH(CH_3)), 18.16 (3CH_3, 3Si-CH(CH_3)), 20.35 (2CH_3, N-CH(CH_3)$_2$), 20.79 (CH_3-24), 21.48 (2CH_3, N-CH(CH_3)$_2$), 28.11 (C-23), 28.12 (C-26), 31.85 (C-24), 34.18 (C-16), 35.52 (C-12), 35.68 (C-22), 41.24 (C-18), 45.44 (N-CH(CH_3)$_2$), 45.83 (C-20), 46.66 (N-CH(CH_3)$_2$), 65.36 (C-19), 67.77 (C-17), 77.89 (C-25), 82.69 (C-13), 97.26 (C-21), 123.51 (C-15), 134.82 (C-10), 138.03 (C-14), 144.44 (C-11), 154.0 (CO).

MS (CI, NH_3) : m/z 797 (MH^+ + NH_3), 780 (MH^+), 750, 736, 606 (100%), 581, 474, 461, 449, 341, 329, 323, 128.

Anal calc for $C_{44}H_{85}O_6NSi_2$, 780.25 : C, 67.72, H, 10.98. Found : C, 68.26, H, 10.75.

• *[2S(2E,6Z,4S,5S),4R,6R,8S,9R] 2-{7-[(*N,N*-Diisopropylcarbamoyl)oxy]-3,5-dimethyl-4-[(triisopropylsilyl)oxy]hepta-2,6-dienyl}-8-isopropyl-9-methyl-4-[(triethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecane*
ent-**28**
*[2S(2E,6Z,4R,5R),4R,6R,8S,9R] 2-{7-[(*N,N*-Diisopropylcarbamoyl)oxy]-3,5-dimethyl-4-[(triisopropylsilyl)oxy]hepta-2,6-dienyl}-8-isopropyl-9-methyl-4-[(triethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecane*
ent-**27**

The Hoppe homoaldolization reaction was carried out on the enantiomeric aldehyde *ent*-**26** (484 mg, 1.13 mmol) under the conditions used above for **26** to give, after column chromatography, the major 4*S*,5*S*-aldol product (527 mg, 74% yield) and its minor 4*R*,5*R*-isomer (79 mg, 11% yield) corresponding to a 4*S*,5*S*/4*R*,5*R* ratio of 87:13.

■ *[2S(2E,6Z,4S,5S),4R,6R,8S,9R] 2-{7-[(*N,N*-Diisopropylcarbamoyl)oxy]-4-hydroxy-3,5-dimethylhepta-2,6-dienyl}-8-isopropyl-9-methyl-4-[(triethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecane (major isomer)*

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.52 (q, J = 8.0 Hz, 6H, Si(CH_2-CH_3)$_3$), 0.72 (d, J = 7.0 Hz, 3H, CH_3), 0.77 (d, J = 7.0 Hz, 3H, CH_3), 0.80 (d, J = 7.0 Hz, 3H, CH_3), 0.87 (d, J = 7.0 Hz, 3H, CH_3), 0.89 (t, J = 8.0 Hz, 9H, Si(CH_2-CH_3)$_3$), 1.19 (m, 12H, 2N-CH(CH_3)$_2$), 1.41-1.63 (m, 6H, CH_2-22 + CH_2-23 + H-24 + H-26), 1.58 (d, J = 1.0 Hz, 3H, CH_3-14), 1.70-1.90 (m, 4H, CH_2-18 + CH_2-20), 2.19 (t, J = 6.9 Hz, 2H, CH_2-16), 2.84 (m, 1H, H-12), 2.97 (dd, J = 9.5, 2.5 Hz, 1H, H-25), 3.50 (m, 1H, H-17), 3.58 (d, J = 9.6 Hz, 1H, H-13), 3.75 (m, 1H, N-CH(CH_3)$_2$), 4.04 (m, 1H, N-CH(CH_3)$_2$), 4.04 (m, 1H, H-19), 4.57 (dd, J = 9.95, 6.4 Hz, 1H, H-11), 5.43 (tq, J = 7.0, 1.0 Hz, 1H, H-15), 7.12 (d, J = 6.0 Hz, 1H, H-10).

■ *2S(2E,6Z,4R,5R),4R,6R,8S,9R] 2-{7-[(*N,N*-Diisopropylcarbamoyl)oxy]-4-hydroxy-3,5-dimethylhepta-2,6-dienyl}-8-isopropyl-9-methyl-4-[(triethylsilyl)oxy]-1,7-dioxaspiro-[5.5]undecane (minor isomer)*

IR ($CHCl_3$) : 3 500-3 400, 1 690, 1 670, 1 520, 1 470, 1 430, 1 300, 1 200.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.58 (q, J = 8.0 Hz, 6H, Si(CH_2-CH_3)$_3$), 0.77 (d, J = 7.0 Hz, 3H, CH_3-26), 0.81 (d, J = 7.0 Hz, 3H, CH_3-26), 0.85 (d, J = 7.0 Hz, 3H, CH_3-12), 0.88 (d, J = 7.0 Hz, 3H, CH_3-24), 0.94 (t, J = 8.0 Hz, 9H, Si(CH_2-CH_3)$_3$), 1.26 (m, 12H, 2N-CH(CH_3)$_2$), 1.40-1.55 (m, 6H, CH_2-22 + H-23b + H-24 + H-26), 1.64 (d, J = 1.0 Hz, 3H, CH_3-14) 1.80-1.90 (m, 4H, CH_2-18 + CH_2-20), 2.18 (ddd, J = 12.5, 7.5, 7.0 Hz, 1H, Ha-16), 2.28 (ddd, J = 12.5, 7.0, 6.5 Hz, 1H, Hb-16), 2.88 (m, 1H, H-12), 3.04 (dd, J = 10.0, 2.5 Hz, 1H, H-25), 3.58 (m, 1H, H-17), 3.64 (d, J = 8.8 Hz, 1H, H-13), 3.70 (m, 1H, N-CH(CH_3)$_2$), 4.10 (m, 1H, N-CH(CH_3)$_2$), 4.10 (m, 1H, H-19), 4.64 (dd, J = 10.0, 6.5 Hz, 1H, H-11), 5.47

(tq, J = 7.0, 1.0 Hz, 1H, H-15), 7.16 (d, J = 6.5 Hz, 1H, H-10).

MS : (CI, NH_3) : m/z 641 ($MH^+ + NH_3$), 624 (MH^+), 606 ($MH^+ - 18$), 594 ($M^+ - 29$), 492 (M^+ - OTES), 479 (M^+ - OTES - 18), 442 ($M^+ - 198 + 17$), 425 ($M^+ - 198$), 341, 293 ($M^+ - 198$ - HOTES), 216 ($199 + NH_3$), 199, 128.

The protection of the secondary hydroxyl group of both the above homoaldols (major and minor) was carried out as described for the natural series to give *ent*-**28** (630 mg, 90% yield) from 527 mg starting material in the case of the major *ent*-isomer, and *ent*-**27** (65 mg, 90% yield) from 60 mg of starting minor non-natural *ent*-aldol.

ent-**28** : $[\alpha]_D = -20.3$ (c = 0.35, $CHCl_3$).

IR ($CHCl_3$) : 1 680, 1 650, 1 510, 1 450, 1 420, 1 200, 1 050.

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.52 (q, J = 8.0 Hz, 6H, Si(CH_2-CH_3)$_3$), 0.72 (d, J = 7.0 Hz, 3H, CH_3), 0.75 (d, J = 7.0 Hz, 3H, CH_3), 0.80 (d, J = 7.0 Hz, 3H, CH_3), 0.89 (t, J = 8.0 Hz, 9H, Si(CH_2-CH_3)$_3$), 0.94 (d, J = 7.0 Hz, 3H, CH_3-12), 0.95 (s wide, 18H, 3Si-CH(CH_3)$_2$), 1.18 (m, 12H, 2N-CH(CH_3)$_2$), 1.40-1.60 (m, 6H, CH_2-22 + CH_2-23 + H-24 + H-26), 1.53 (d, J = 1.0 Hz, 3H, CH_3-14), 1.70-1.80 (m, 4H, CH_2-18 + CH_2-20), 2.14 (m, 2H, CH_2-16), 2.84 (m, 1H, H-12), 2.98 (dd, J = 8.0, 1.5 Hz, 1H, H-25), 3.48 (m, 1H, H-17), 3.72 (m, 1H, N-CH(CH_3)$_2$), 3.84 (d, J = 8.0 Hz, 1H, H-13), 4.04 (m, 2H, N-CH(CH_3)$_2$ + H-19), 4.58 (dd, J = 9.9, 6.6 Hz, 1H, H-11), 5.31 (t, J = 7.0 Hz, 1H, H-15), 6.97 (dd, J = 6.5, 0.6 Hz, 1H, H-10).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 4.88 (3C, Si-CH_2-CH_3), 6.80 (3CH_3, Si-CH_2-CH_3), 11.92 (CH_3-14), 12.57 (3C, Si-CH(CH_3)$_2$), 14.06 (CH_3-26), 17.34 (CH_3-12), 17.58 (CH_3-26), 18.12 (3CH_3, 3Si-CH-(CH_3)) 18.16 (3CH_3, 3Si-CH-(CH_3)), 20.25 (CH_3, N-CH(CH_3)$_2$), 20.79 (CH_3-24), 21.48 (CH_3, N-CH(CH_3)$_2$), 28.11 (C-23), 28.12 (C-26), 31.84 (C-24), 34.18 (C-16), 35.52 (C-12), 35.67 (C-22), 41.24 (C-18), 45.44 (N-CH(CH_3)$_2$), 45.83 (C-20), 46.66 (N-CH(CH_3)$_2$), 65.36 (C-19), 67.77 (C-17), 77.89 (C-25), 82.69 (C-13), 97.26 (C-21), 123.51 (C-15), 134.82 (C-10), 138.03 (C-14), 144.44 (C-11), 152.98 (C=O).

MS (CI, NH_3) : m/z 797, 780, 730, 606, 581, 474, 449.

Anal calc for $C_{44}H_{85}O_6NSi_2$, 780.25 : C, 67.72, H, 10.98, N, 1.79. Found : C, 67.61, H, 11.12, N, 1.76.

ent-**27** : IR ($CHCl_3$) : 1 680, 1 650, 1 510, 1 460, 1 430, 1 200, 1 050.

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.52 (q, J = 8.0 Hz, 6H, Si(CH_2-CH_3)$_3$), 0.72 (d, J = 7.0 Hz, 3H, CH_3-24), 0.76 (d, J = 7.0 Hz, 3H, CH_3-26), 0.81 (d, J = 7.0 Hz, 3H, CH_3-26), 0.90 (t, J = 8.0 Hz, 9H, Si(CH_2-CH_3)$_3$), 0.95 (s wide, 6H, Si-CH(CH_3)$_2$), 0.96 (d, J = 7.0 Hz, 3H, CH_3-12), 0.98 (s wide, 12H, 2Si-CH(CH_3)$_2$), 1.18 (m, 12H, 2N-CH(CH_3)$_2$), 1.40-1.60 (m, 6H, CH_2-22 + CH_2-23 + H-24 + H-26), 1.56 (d, J = 1.0 Hz, 3H, CH_3-14), 1.70-1.80 (m, 4H, CH_2-18 + CH_2-20), 2.14 (t, J = 7.0 Hz, 2H, CH_2-16), 2.84 (m, 1H, H-12), 2.97 (dd, J = 9.7, 2.5 Hz, 1H, H-25), 3.49 (m, 1H, H-17), 3.68 (m, 1H, N-CH(CH_3)$_2$), 3.86 (d, J = 7.3 Hz, 1H, H-13), 4.04 (m, 1H, N-CH(CH_3)$_2$), 4.04 (m, 1H, H-19), 4.58 (dd, J = 9.8, 6.5 Hz, 1H, H-11), 5.31 (tq, J = 7.0, 1.0 Hz, 1H, H-15), 6.97 (dd, J = 6.5, 0.6 Hz, 1H, H-10).

MS (CI, NH_3) : m/z 797 ($MH^+ + NH_3$), 780 (MH^+), 750, 736 ($M^+ - 43$), 606 (M^+ - HOTIPS), 581 ($M^+ - 198$), 474 (M^+ - OTES - HOTIPS), 449 ($M^+ - 199$ - HOTES), 341, 323, 293, 199, 128.

• *[2R(2E,4S,5S),4S,6S,8R,9S] 8-Isopropyl-9-methyl-2-{3,5-dimethyl-4-[(triisopropylsilyl)oxy]hept-2-en-6-ynyl}-4-[(triethylsilyl)oxy]-1,7-dioxaspiro[5.5]undecane* **29**

A solution of n-BuLi (1.5 M, 0.64 mL, 3 equiv) was slowly added at −78°C to a solution of vinyl carbamate **27** (250 mg, 0.32 mmol) in diethyl ether (5 mL). After 30 min at −78°C, the temperature was allowed to reach −30°C and another equivalent of n-BuLi was added (0.21 mL). After stirring for 20 min, the reaction mixture was added with aqueous NH_4Cl and extracted with diethyl ether. The combined organic phases were washed with brine, dried on $MgSO_4$ and the solvent evaporated. The crude product was purified on silica gel column (hexane/diethyl ether mixtures from 100:0 to 85:15) to give the acetylenic derivative **29** (140 mg, 69%). $[\alpha]_D = +48.5$ (c = 1.28, $CHCl_3$).

IR ($CHCl_3$) : 3 305, 3 020, 2 970, 2 870, 2 400, 1 530, 1 460, 1 390, 1 220, 1 010, 990.

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.52 (q, J = 8.0 Hz, 6H, Si(CH_2-CH_3)$_3$), 0.72 (d, J = 6.0 Hz, 3H, CH_3), 0.76 (d, J = 7.0 Hz, 3H, CH_3), 0.81 (d, J = 7.0 Hz, 3H, CH_3), 0.90 (t, J = 8.0 Hz, 9H, Si(CH_2-CH_3)$_3$), 0.97 (d, J = 8.0 Hz, 3H, CH_3-12), 0.99 (s wide, 21H, 3CH + 3CH_3, 3Si-CH(CH_3)$_2$), 1.14 (m, 6H, CH_2-22 + CH_2-23 + H-24 + H-26), 1.54 (d, J = 1.0 Hz, 3H, CH_3-14), 1.78 (m, 4H, CH_2-18 + CH_2-20), 1.94 (d, J = 2.5 Hz, 1H, H-10), 2.12 (m, 2H, CH_2-16), 2.54 (qdd, J = 7.5, 7.5, 2.5 Hz, 1H, H-12), 2.97 (dd, J = 9.5, 2.0 Hz, 1H, H-25), 3.48 (m, 1H, H-17), 4.03 (m, 1H, H-19), 4.03 (d, J = 7.7 Hz, 1H, H-13), 5.39 (tq, J = 7.0, 1.0 Hz, 1H, H-15).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 4.8 (3C, 3Si-CH_2-CH_3), 6.68 (3CH_3, 3Si-CH_2-CH_3), 12.0 (CH_3-14), 12.41 (3C, Si-CH(CH_3)$_2$), 13.93 (CH_3-26), 17.17 (CH_3-12), 17.01 (CH_3-26), 18.02 (3CH_3, 3Si-CH(CH_3)), 18.05 (3CH_3, 3Si-CH(CH_3)), 20.63 (CH_3-24), 28.02 (C-23), 28.14 (C-26), 31.56 (C-24), 31.99 (C-12), 34.04 (C-16), 35.62 (C-22), 41.25 (C-18), 45.52 (C-20), 65.24 (C-19), 67.59 (C-17), 69.2 (C-10), 77.83 (C-25), 81.32 (C-13), 87.7 (C-11), 97.16 (C-21), 124.29 (C-15), 136.58 (C-14).

MS : (CI, NH_3) : m/z 652 ($MH^+ + NH_3$), 635 (MH^+), 591 ($M^+ - 43$), 581 ($M^+ - 53$), 503 (M^+ - OTES), 461 (M^+ - OTIPS), 449 (M^+ - HOTES), 341, 329, 323, 235.

Anal calc for $C_{37}H_{70}O_4Si_2$, 635.05 : C, 69.97, H, 11.11. Found C, 70.11, H, 11.15.

• *[2R(2E,4S,5S),4S,6S,8R,9S] 2-(4-Hydroxy-3,5-dimethylhept-2-en-6-ynyl)-4-hydroxy-8-isopropyl-9-methyl-1,7-dioxaspiro[5.5]undecane* **30**

The bis-silylated acetylenic ether **29** (707 mg, 1.12 mmol) dissolved in THF (10 mL) was treated at 0°C with 5.6 mL of a 1 N Bu_4NF/THF solution. The solution was stirred for 2 h at 0°C, and then for 6 h at room temperature before being concentrated *in vacuo*. The oily residue was submitted to a MPLC purification (Silica gel Lichroprep Merck Art 9336, elution with ethyl acetate/petroleum ether from 20:80 to 100:0) to afford 426 mg of the expected diol **30** (98% yield). $[\alpha]_D = +61$ (c = 1.05, $CHCl_3$).

IR ($CHCl_3$) : 3 540, 3 430, 3 305, 2 970-2 960, 2 870, 1 450, 1 380, 1 360, 1 250, 1 175, 1 010, 980.

^1H NMR ($CDCl_3$, 250 MHz), δ : 0.78 (d, J = 6.0 Hz, 3H, CH_3), 0.81 (d, J = 7.0 Hz, 3H, CH_3), 0.94 (d, J = 7.0 Hz, 3H, CH_3), 1.11 (d, J = 7.0 Hz, 3H, CH_3), 1.63 (d, J = 1.0 Hz, 3H, CH_3-14), 1.0-2.1 (m, 10H), 2.16 (d, J = 2.4 Hz, 1H, H-10), 2.25 (dd, J = 14.8, 7.9 Hz, 1H, Ha-16), 2.32 (dd, J = 14.8, 6.9 Hz, 1H, Hb-16), 2.66 (qdd, J = 7.5, 7.5, 2.4 Hz, 1H, H-12), 3.04 (dd, J = 9.4, 2.2 Hz, 1H, H-25), 3.61 (m, 1H, H-17), 3.84 (d, J = 8.0 Hz, 1H, H-13), 4.11 (tt, J = 11.2, 4.7 Hz, 1H, H-19), 5.53 (t wide, J = 7.0 Hz, 1H, H-15).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 11.45 (CH_3-14), 14.17 (CH_3-26), 17.46 (CH_3-12), 17.72 (CH_3-26), 20.86 (CH_3-24), 28.20 (C-23), 28.29 (C-26), 31.14 (C-24), 31.66 (C-12), 34.18 (C-22), 35.81 (C-16), 40.70 (C-18), 45.06 (C-20), 64.96 (C-19), 67.67 (C-17), 70.78 (C-10), 78.18 (C-25), 81.00 (C-13), 86.09 (C-11), 97.35 (C-21), 125.6 (C-15), 135.75 (C-14).

MS (CI, NH_3) : m/z 382 ($MH^+ + NH_3$), 365 (MH^+), 347 , 329, 311, 293, 227, 110.

• *[2R(2E,6E)4S,5S,4S,6S,8R,9S] 2-[(4-Hydroxy-3,5-dimethyl-7-tributylstannyl)hepta-2,6-dienyl]-8-isopropyl-9-methyl-1,7-dioxaspiro[5.5]undecan-4-ol* **31**

Diol **30** (354 mg, 0.97 mmol) in solution in dry toluene (20 mL) was treated with Bu_3SnH (0.45 mL, 1.7 equiv) and azoisobutyronitrile (AIBN, 10 mg, 0.05 equiv). The reaction mixture was refluxed for 10 h under argon and the solvent removed under vacuum to give a crude product which was shown from ^{1}H NMR to contain a 85:15 mixture of *E/Z* vinylstannanes **31**. MPLC purification on silica gel (pre-treated with 1% Et_3N in petroleum ether, elution with diethyl ether/petroleum ether from 0:100 to 20:80) allowed isolation of pure **31**-*E* isomer. $[\alpha]_D$ = +25 (*c* = 2.2, $CHCl_3$).

IR ($CHCl_3$) : 3 680, 3 510, 3 020, 2 960, 2 920, 2 400, 1 590, 1 540, 1 460, 1 430, 1 370, 1 220, 1 010, 980, 930, 830-750.

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.78 (d, *J* = 6.0 Hz, 3H, CH_3), 0.82 (d, *J* = 7.0 Hz, 3H, CH_3), 0.88 (d, *J* = 7.0 Hz, 3H, CH_3), 0.89 (t, *J* = 6.5 Hz, 9H, 3 Sn-$(CH_2)_3$-CH_3), 0.91 (d, *J* = 7.0 Hz, 3H, CH_3), 0.92 (t, *J* = 6.5 Hz, 6H, 3 Sn-CH_2), 1.10-1.50 (m, 18H, 3Sn-CH_2-CH_2 + 3Sn-CH_2-CH_2-CH_2 + CH_2-22 + CH_2-23 + CH-24 + CH-26), 1.64 (d, *J* = 1.0 Hz, 3H, CH_3-14), 1.60-2.4 (m, 7H, CH_2-16 + CH_2-18 + CH_2-20 + CH-12), 3.06 (dd, *J* = 9.4, 2.2 Hz, 1H, H-25), 3.62 (m, 1H, H-17), 4.12 (m, 1H, H-19), 5.47 (t wide, *J* = 7.0 Hz, 1H, H-15), 5.81 (dd, *J* = 18.9, 7.9 Hz, 1H, H-11), 6.11 (d, *J* = 18.9 Hz, 1H, H-10).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 9.60 (3C, 3Sn-CH_2), 13.78 ($3CH_3$, 3Sn-$(CH_2)_3$-CH_3), 11.27 (CH_3-14), 14.20 (CH_3-26), 17.08 (CH_3-12), 17.46 (CH_3-26), 20.87 (CH_3-24), 27.30 (3C, 3Sn-CH_2-CH_2), 28.23 (C-23), 28.34 (C-26), 29.2 (3C, 3Sn-CH_2-CH_2-CH_2), 31.73 (C-24), 34.27 (C-16), 35.88 (C-22), 40.79 (C-20), 45.14 (C-18), 46.80 (C-12), 65.08 (C-19), 67.80 (C-17), 78.15 (C-25), 81.11 (C-13), 97.36 (C-21), 125.33 (C-15), 131.37 (C-11), 136.48 (C-14), 151.67 (C-10).

MS (CI, NH_3) : m/z 657 (MH^+, for the ^{120}Sn major isotope), 639 (M^+ - 15), 621, 599, 445, 349, 331, 308.

• *(3E,3aS,4R,6S,7S,7aR) Methyl 3a-hydroxy-3-iodomethylidene-6,7-isopropylidenedioxy-6-methyl-octahydrobenzofuran-4-carboxylate* **38**

To a well-stirred solution of vinylstannane derivative **37** [6] (278 mg, 0.47 mmol) in dichloromethane (1 mL) was added dropwise a solution of iodine (133 mg, 0.52 mmol) in dichloromethane (0.5 mL). The addition was stopped when a red color apeared and, after persistence of the color for 20 min, the reaction mixture was filtered over silica. Elution with diethyl ether followed by evaporation of the filtrate under reduced pressure and purification by column chromatography (silica, hexane/ethyl acetate, from 1:0 to 0:1) gave the desired iodo derivative **38** (210 mg, 90% yield) which was pure enough to be used in the next step without further purification. $[\alpha]_D$ = +16.2 (*c* = 1.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 1.32 (s, 3H, CH_3-4), 1.36 (s, 3H, CH_3 acetonide), 1.53 (s, 3H, CH_3 acetonide), 1.93 (dd, *J* = 13.2, 12.0 Hz, 1H, Ha-3), 2.11 (dd, *J* = 12.0, 4.1 Hz, 1H, Hb-3), 2.69 (dd, *J* = 13.2, 4.1 Hz, 1H, H-2), 3.73 (s, 3H, $COOCH_3$), 3.78 (d, *J* = 2.6 Hz, 1H, H-5), 4.20 (d, *J* = 2.6 Hz, 1H, H-6), 4.32 (dd, *J* = 15.3, 2.7 Hz, 1H, Ha-8a), 4.42 (dd, *J* = 15.3, 2.7 Hz, 1H, Hb-8a), 5.64 (s, 1H, OH-7), 6.23 (t, *J* = 2.7 Hz, 1H, H-9).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : 21.44 (CH_3-4), 26.50 and 28.03 (2 CH_3 acetonide), 37.24 (C-3), 44.57 (C-2) 52.60 ($COOCH_3$), 71.57 (C-5), 75.18 (C-8a), 77.29 (C-4), 79.20 (C-6), 81.11 (C-7), 81.31 (C-9), 109.08 (O-$(CH_3)_2C$-O), 154.12 (C-8), 175.36 (C-1).

Anal calc for $C_{15}H_{21}O_6I$, 424.22 : C, 42.47, H, 4.99 Found : C, 42.06, H, 5.12.

• *(3E,3aS,4R,6S,7S,7aR) [2-(Trimethylsilyl)ethyl] 3a-hydroxy-3-iodomethylidene-6,7-isopropylidenedioxy-6-methyl-octahydrobenzofuran-4-carboxylate* **39**

This reaction was carried out according to Seebach's procedure [27].

The above methyl ester **38** (210 mg, 0.495 mmol) was treated with 2-(trimethylsilyl)ethanol (TSE, 586 mg, 0.72 mL, 4.95 mmol) and titanium (IV) isopropoxide (42 mg, 0.044 mL, 0.14 mmol). The reaction mixture was heated at 100°C for 6 h. After cooling to room temperature, hexane (2 mL) was added and the resulting mixture was poured over a pad of silica. Elution with hexane/diethyl ether (from 1:0 to 1:1) gave the desired TSE-ester **39** (226 mg, 90% yield). $[\alpha]_D$ = +8.0 (*c* = 1.45, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.04 (s, 9H, $3CH_3$, $(CH_3)_3$-Si), 0.98 (m, 2H, CH_2-2′), 1.34 (s, 3H, CH_3-4), 1.38 (s, 3H, CH_3 acetonide), 1.55 (s, 3H, CH_3-acetonide), 1.90 (dd, *J* = 13.2, 12.1 Hz, 1H, Ha-3), 2.12 (dd, *J* = 21.1, 4.1 Hz, 1H, Hb-3), 2.64 (dd, *J* = 13.2, 4.1 Hz, 1H, H-2), 3.80 (d, *J* = 2.6 Hz, 1H, H-5), 4.20 (d, *J* = 2.6 Hz, 1H, H-6), 4.23 (m, 2H, CH_2-1′), 4.33 (dd, *J* = 15.0, 2.7 Hz, 1H, Ha-8a), 4.44 (dd, *J* = 15.0, 2.7 Hz, 1H, Hb-8a), 5.80 (s, 1H, OH-7), 6.24 (t, *J* = 2.7 Hz, 1H, H-9).

MS (EI) : m/z 495 (M^+ - 15), 467, 449, 355, 162, 128, 73, 43.

HRMS : $M^+ - CH_3$ (calc for $C_{18}H_{28}O_6SiI$: 495.0702, found : 495.0697.

Anal calc for $C_{19}H_{31}O_6SiI$, 510.42 : C 44.70, H 6.12. Found : C 45.10, H 6.28.

• *(3E,3aS,4R,7R,7aR) [2-(Trimethylsilyl)ethyl] 7-[(t-butyldimethylsilyl)oxy]-3a-hydroxy-3-iodomethylidene-6-methyl-2,3,3a,4,7,7a-hexahydrobenzofuran-4-carboxylate* **40**

The acetoxy methyl ester **32** [6] (50 mg, 96 μmol) was treated with 2-(trimethylsilyl)-ethanol (248 mg, 300 μL, 2.09 mmol) and titanium (IV) isopropoxide (7.1 mg, 8.6 μL, 25 μmol) according to the same procedure as above to give after purification the pure TSE-ester **40** (50 mg, 92% yield). $[\alpha]_D$ = −23.7 (*c* = 2.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.07 (s, 9H, $(CH_3)_3$-Si), 0.14 (2s, 6H, $2CH_3$, $(CH_3)_2$-Si), 0.93 (s, 9H, $3CH_3$, $(CH_3)_3$C-Si), 1.04 (m, 2H, CH_2-2′), 1.82 (m, 3H, CH_3-4), 3.41 (m, *J* = 2.6 Hz, 1H, H-2), 3.98 (d, *J* = 4.8 Hz, 1H, H-5), 4.27 (m, 2H, CH_2-1′), 4.38 (dd, *J* = 15.0, 2.6 Hz, 1H, Ha-8a), 4.44 (m, 1H, H-6), 4.48 (dd, *J* = 15.0, 2.6 Hz, 1H, Hb-8a), 5.14 (s, 1H, OH-7), 5.43 (dm, *J* = 2.6, 1.5 Hz, 1H, H-3), 6.30 (t, *J* = 2.6 Hz, 1H, H-9).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : −4.60 and −4.91 ($2CH_3$, $(CH_3)_2$-Si), 1.53 ($3CH_3$, $(CH_3)_3$-Si), 17.3 (C-2′), 18.3 (C, $(CH_3)_3C$-Si)), 20.0 (CH_3-4), 25.8 ($3CH_3$, $(CH_3)_3$C-Si), 45.7 (C-2), 64.2 (C-1′), 69.2 (C-5), 70.2 (C-6), 74.7 (C-8a), 80.7 (C-7), 83.6 (C- 9), 117.4 (C-3), 137.3 (C-4), 155.6 (C-8), 173.9 (C-1).

MS (CI, NH_3) : m/z 584 (MH^+ + 17), 567 (MH^+), 521, 481, 389, 361, 331, 315.

Coupling reactions between the "Southern" and "Northern" parts of 22,23-dihydroavermectin B1b **1**

• *General procedure (described on a 0.10 mmol scale)* An oven-dried 10 mL flask was charged under argon with bis-acetonitrile palladium (II) chloride (0.02 mmol, 0.2 equiv) and *N*,*N*-dimethylformamide (500 μL). To this yellow solution was introduced a solution of the "south" fragment (0.10 mmol) in *N*,*N*-dimethylformamide (500 μL). This mixture was stirred for 10 min at room temperature then cooled to 0°C. A solution of the "north" fragment (0.12 mmol) in *N*,*N*-dimethylformamide (500 μL) was added slowly (over 30 min) *via* a syringe-pump. Aluminium foil was used to protect the flask from light. The reaction was followed by TLC (hexane/ethyl acetate : 1:1); it was generally complete within 4 h. A saturated aqueous ammonium chloride solution (1 mL) was added, and then diethyl ether (2 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 2 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC on silica gel (light petroleum ether/diethyl ether, 2:3) to give, in order of increasing R_f values, the expected 8*E*,10*Z*-diene, its 8*E*,10*E* isomer and the remaining starting "south" fragment.

• *{3E[2E,6E,4S,5S,(2R,4S,6S,8R,9S)], 3aS,4R,6S,7S,7aR} [2-(Trimethylsilyl) ethyl] 3a,6,7-trihydroxy-3-{5-hydroxy-8-[4-hydroxy-8-isopropyl-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl]-4,6-dimethylocta-2,6-dienylidene}-6-methyl-octahydrobenzofuran-4-carboxylate* **41**
{3E[2Z,6E,4S,5S,(2R,4S,6S,8R,9S)], 3aS,4R,6S,7S,7aR} [2-(Trimethylsilyl) ethyl] 3a,6,7-trihydroxy-3-{5-hydroxy-8-[4-hydroxy-8-isopropyl-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl]-4,6-dimethylocta-2,6-dienylidene}-6-methyl-octahydrobenzofuran-4-carboxylate **42**

The 4,5-isopropylidenedioxy "south" fragment **39** (9.9 mg, 19 μmol) and the "north" fragment **31** (85:15 *E*/*Z* mixture, 16.3 mg, 23 μmol) were treated according to the general procedure to give after aqueous ammonium chloride work-up and preparative TLC, 8*E*,10*Z*-**42** (2.5 mg, 18% yield) and 8*E*,10*E* **41** (7.4 mg, 55% yield) in order of increasing R_f. Under these conditions, the acetonide protecting group was removed.

41 : ^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.02 (s, 9H, $3CH_3$, $(CH_3)_3$-Si), 0.75 (d, *J* = 5.5 Hz, 3H, CH_3-26), 0.79 (d, *J* = 7.0 Hz, 3H, CH_3-26), 0.87 (d, *J* = 7.0 Hz, 3H, CH_3-24), 0.92 (d, *J* = 6.2 Hz, 3H, CH_3-12), 0.96 (m, 2H, CH_2-2′), 1.00-1.65 (m, 8H), 1.37 (s, 3H, CH_3-4), 1.61 (s, 3H, CH_3-14), 1.75-2.12 (m, 5H), 2.29 (m, 2H, CH_2-16), 2.64 (dd, *J* = 13.8, 3.8 Hz, 1H, H-2), 2.92 (d, wide, *J* = 8.8 Hz, 1H, H-25), 3.54 (m, 1H, H-17), 3.66 (d, *J* = 8.8 Hz, 1H, H-13), 3.87 (d, wide, *J* = 4.5 Hz, 1H, H-5), 3.91 (d, *J* = 4.5 Hz, 1H, H-6), 4.08 (m, 1H, H-19), 4.19 (m, 2H, CH_2-1′), 4.58 (s, wide, 2H, CH_2-8a), 5.42 (t, *J* = 7.5 Hz, 1H, H-15), 5.61 (dd, *J* = 14.0, 8.0 Hz, 1H, H-11), 5.84 (dd, *J* = 14.0, 11.2 Hz, 1H, H-10), 6.21 (d, wide, *J* = 11.2 Hz, 1H, H-9).

MS (CI, NH_3) : *m*/*z* 708 (M^+), 691, 673, 663, 573, 555, 353, 311.

42 : ^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.02 (s, 9H, $3CH_3$, $(CH_3)_3$-Si), 0.76 (d, *J* = 6.0 Hz, 3H, CH_3-26), 0.80 (d, *J* = 6.8 Hz, 3H, CH_3-26), 0.88 (d, *J* = 6.8 Hz, 3H, CH_3-24), 0.92 (d, *J* = 6.2 Hz, 3H, CH_3-12), 0.96 (m, 2H, CH_2-2′), 1.00-1.65 (m, 8H), 1.38 (s, 3H, CH_3-4), 1.65 (s, 3H, CH_3-14), 1.75-2.12 (m, 5H), 2.25 (m, 2H, CH_2-16), 2.67 (dd, *J* = 13.0, 3.8 Hz, 1H, H-2), 3.02 (d, wide, *J* = 8.8 Hz, 1H, H-25), 3.55 (m, 1H, H-17), 3.75 (d, *J* = 7.5 Hz, 1H, H-13), 3.90 (d, wide, *J* = 4.5 Hz, 1H, H-5), 3.94 (d, *J* = 4.5 Hz, 1H, H-6), 4.07 (m, 1H, H-19), 4.20 (m, 2H, CH_2-1′), 4.62 (d, wide, *J* = 2.0 Hz, 2H, CH_2-8a), 5.45 (m, 1H, H-15), 5.46 (dd, *J* = 11.2, 6.2 Hz, 1H, H-11), 5.86 (t, *J* = 11.2 Hz, 1H, H-10), 6.21 (dt, *J* = 11.2, 2.0 Hz, 1H, H-9).

MS (CI, NH_3) : *m*/*z* 726 (MH^+ + 17), 708 (M^+), 691, 673, 663, 645, 573, 555, 353, 311.

• *{3E[2E,6E,4S,5S,(2R,4S,6S,8R,9S)], 3aS,4R,6S,7S,7aR} [2-(Trimethylsilyl) ethyl] 3a-hydroxy-3-{5-hydroxy-8-[4-hydroxy-8-isopropyl-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl]-4,6-dimethylocta-2,6-dienylidene}-6,7-isopropylidenedioxy-6-methyl-octahydrobenzofuran-4-carboxylate* **43**
{3E[2Z,6E,4S,5S,(2R,4S,6S,8R,9S)], 3aS,4R,6S,7S,7aR} [2-(Trimethylsilyl) ethyl] 3a-hydroxy-3-{5-hydroxy-8-[4-hydroxy-8-isopropyl-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl]-4,6-dimethylocta-2,6-dienylidene}-6,7-isopropylidenedioxy-6-methyl-octahydrobenzofuran-4-carboxylate **44**

The above 4,5-isopropylidenedioxy "south" fragment **39** (28.5 mg, 56 μmol) and "north" fragment **31** (*E*/*Z* mixture, 40.0 mg, 61 μmol) were treated according to the general procedure except that, at the end of the reaction, the mixture was treated with a 9:1 mixture of brine and saturated aqueous sodium bicarbonate solution instead of saturated aqueous ammonium chloride. The dienes 8*E*,10*Z*-**44** (6.3 mg, 15% yield) and 8*E*,10*E*-**43** (16.7 mg, 40% yield) were isolated with, in this case, no removal of the acetonide protecting group.

43 : ^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.02 (s, 9H, $3CH_3$, $(CH_3)_3$-Si), 0.76 (d, *J* = 5.9 Hz, 3H, CH_3-26), 0.79 (d, *J* = 6.8 Hz, 3H, CH_3-26), 0.87 (d, *J* = 6.8 Hz, 3H, CH_3-24), 0.92 (d, *J* = 7.1 Hz, 3H, CH_3-12), 0.97 (m, 2H, CH_2-2′), 1.02-1.60 (m, 8H), 1.34 (s, 3H, CH_3-4), 1.39 (s, 3H, CH_3-acetonide), 1.55 (s, 3H, CH_3-acetonide), 1.61 (s, 3H, CH_3-14), 1.90 (m, 5H), 1.95 (dd, *J* = 12.8, 12.1 Hz, 1H, Ha-3), 2.10 (dd, *J* = 12.1, 2.8 Hz, 1H, Hb-3), 2.27 (m, 2H, CH_2-16), 2.66 (dd, *J* = 12.8, 3.8 Hz, 1H, H-2), 3.02 (dd, *J* = 8.8, 2.0 Hz, 1H, H-25), 3.59 (m, 1H, H-17), 3.66 (d, *J* = 8.9 Hz, 1H, H-13), 3.88 (d, *J* = 2.6 Hz, 1H, H-5), 4.09 (m, 1H, H-19), 4.10 (d, *J* = 2.6 Hz, 1H, H-6), 4.21 (m, 2H, CH_2-1′), 4.64 (d, wide, *J* = 2.0 Hz, 2H, CH_2-8a), 5.44 (t wide, *J* = 6.8 Hz, 1H, H-15), 5.64 (dd, *J* = 12.5, 8.1 Hz, 1H, H-11), 5.67 (s, 1H, OH), 5.93 (t, *J* = 12.5 Hz, 1H, H-10), 6.22 (dt, *J* = 12.5, 2.0 Hz, 1H, H-9).

MS (CI, NH_3) : *m*/*z* 749 (MH^+), 713, 691, 673, 663, 645, 627, 573, 555, 353, 311, 118.

44 : ^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.03 (s, 9H, $3CH_3$, $(CH_3)_3$-Si), 0.76 (d, *J* = 5.5 Hz, 3H, CH_3-26), 0.79 (d, *J* = 7.0 Hz, 3H, CH_3-26), 0.87 (d, *J* = 7.0 Hz, 3H, CH_3-24), 0.92 (d, *J* = 7.0 Hz, 3H, CH_3-12), 0.97 (m, 2H, CH_2-2′), 1.02-1.60 (m, 8H), 1.34 (s, 3H, CH_3-4), 1.39 (s, 3H, CH_3-acetonide), 1.55 (s, 3H, CH_3-acetonide), 1.66 (s, 3H, CH_3-14), 1.75-2.12 (m, 5H), 2.25 (m, 2H, CH_2-16), 2.66 (dd, *J* = 13.0, 3.8 Hz, 1H, H-2), 3.02 (dd, *J* = 10.0, 2.0 Hz, 1H, H-25), 3.55 (m, 1H, H-17), 3.76 (d, *J* = 8.0 Hz, 1H, H-13), 3.90 (d, *J* = 2.5 Hz, 1H, H-5), 4.07 (m, 1H, H-19), 4.12 (d, *J* = 2.5 Hz, 1H, H-6), 4.20 (m, 2H, CH_2-1′), 4.62 (d wide, *J* = 2.0 Hz, 2H, CH_2-8a), 5.44 (t,

J = 7.5 Hz, 1H, H-15), 5.45 (dd, J = 11.2, 8.0 Hz, 1H, H-11), 5.86 (t, J = 11.2 Hz, 1H, H-10), 6.22 (dt, J = 11.2, 2.0 Hz, 1H, H-9).

MS (CI, NH_3) : m/z 766 (MH^+ + 17), 749, 708, 691, 673, 655, 645, 627, 573, 555, 353, 334, 311.

• *{3E[2E,6E,4S,5S,(2R,4S,6S,8R,9S)], 3aS,4R,7R,7aR} [2-(Trimethylsilyl) ethyl] 7-[(t-butyldimethylsilyl)oxy]-3a-hydroxy-3-{5-hydroxy-8-[4-hydroxy-8-isopropyl-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl]-4,6-dimethylocta-2,6-dienylidene}-6-methyl-2,3,3a,4,7,7a-hexahydrobenzofuran-4-carboxylate* **45**

{3E[2Z,6E,4S,5S,(2R,4S,6S,8R,9S)], 3aS,4R,7R,7aR} [2-(Trimethylsilyl) ethyl] 7-[(t-butyldimethylsilyl)oxy]-3a-hydroxy-3-{5-hydroxy-8-[4-hydroxy-8-isopropyl-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl]-4,6-dimethylocta-2,6-dienylidene}-6-methyl-2,3,3a,4,7,7a-hexahydrobenzofuran-4-carboxylate **46**

The 3,4-unsaturated "south" fragment **40** (37.0 mg, 65 μmol) and the "north" fragment **31** (85:15 E/Z mixture, 51.0 mg, 78 μmol) were treated according to the general procedure to give, after preparative TLC, the 8E,10Z-diene **46** (6.5 mg, 12% yield) and 8E,10E-diene **45** (20.1 mg, 38% yield) as well as unreacted "south" fragment **40** (5.0 mg, 14% yield). The ^{1}H NMR spectrum of the crude reaction product showed the EE/EZ ratio to be 3:1.

45 : $[\alpha]_D$ = −6.3 (c = 1.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 250 MHz), (interpreted with the help of COSY experiments), δ : 0.03 (s, 9H, $3CH_3$, $(CH_3)_3$-Si), 0.10 and 0.11 (2s, 6H, $2CH_3$, $(CH_3)_2$-Si), 0.76 (d, J = 5.9 Hz, 3H, CH_3-26), 0.80 (d, J = 6.8 Hz, 3H, CH_3-26), 0.88 (d, J = 7.0 Hz, 3H, CH_3-24), 0.90 (s, 9H, $(CH_3)_3$C-Si), 0.92 (d, J = 7.5 Hz, 3H, CH_3-12), 0.97 (m, 2H, CH_2-2′), 1.07-1.28 (m, 6H), 1.44 (m, 1H, H-26), 1.46 (m, 1H, H-24), 1.47 (s, 2H), 1.60 (m, 2H), 1.62 (s, 3H, CH_3-14), 1.78 (s, wide, 3H, CH_3-4), 1.83 (m, 1H, Ha-20), 1.95 (m, 1H, H-12), 2.28 (m, 2H, CH_2-16), 3.03 (dd, J = 8.8, 2.5 Hz, 1H, H-25), 3.39 (m, 1H, H-2), 3.58 (m, 1H, H-17), 3.68 (d, J = 8.6 Hz, 1H, H-13), 3.90 (d, J = 4.9 Hz, 1H, H-5), 4.09 (m, 1H, H-19), 4.20 (m, 2H, CH_2-1′), 4.47 (m, 1H, H-6), 4.63 (d, wide, J = 1.8 Hz, 2H, CH_2-8a), 5.40 (m, 1H, H-3), 5.45 (t, J = 7.5 Hz, 1H, H-15), 5.62 (dd, J = 14.3, 8.4 Hz, 1H, H-11), 5.95 (dd, J = 14.3, 11.0 Hz, 1H, H-10), 6.06 (dt, J = 11.0, 1.8 Hz, 1H, H-9).

^{13}C NMR ($CDCl_3$, 100,57 MHz), δ : −4.92 and −4.59 ($2CH_3$, $(CH_3)_2$-Si), 1.54 ($3CH_3$, $(CH_3)_3$-Si), 11.35 (CH_3-14), 14.09 (CH_3-26), 17.11 (CH_3-24), 17.26 (C-2′), 17.40 (CH_3-12), 18.30 (1C, $(CH_3)_3C$-Si), 19.91 (CH_3-4), 20.79 (CH_3-26), 25.81 ($3CH_3$, $(CH_3)_3$C-Si), 28.12 (C-23), 28.24 (C-26), 31.59 (C-24), 34.06 (C-16), 35.75 (C-22) 40.64 (C-18), 41.37 (C-12), 45.02 (C-20), 46.56 (C-2), 63.84 (C-1′), 64.99 (C-19), 67.65 (C-17), 68.70 (C-8a), 69.32 (C-5), 78.12 (C-25), 78.49 (C-7), 81.70 and 83.04 (C-6 and C-13), 97.27 (C-21), 117.60 (C-3), 119.14 (C-9), 125.10 (C-15), 127.07 (C-10), 136.69 (C-14), 137.76 (C-4), 138.20 (C-11), 144.09 (C-8), 173.94 (C-1).

MS (CI, NH_3) : m/z 822 (MH^+ + 17), 803 (M^+ − 1), 787, 759, 669, 637, 619, 345, 311.

MS (EI) : 805, 787, 769, 655, 637 (100%), 618.

46 : ^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.02 (s, 9H, $3CH_3$, $(CH_3)_3$-Si), 0.11 (s, wide, 6H, $2CH_3$, $(CH_3)_2$-Si), 0.76 (d, J = 5.9 Hz, 3H, CH_3-26), 0.80 (d, J = 6.8 Hz, 3H, CH_3-26), 0.89 (d, J = 6.0 Hz, 3H, CH_3-24), 0.90 (s, 9H, $3CH_3$, $(CH_3)_3$C-Si), 0.91 (d, J = 6.8 Hz, 3H, CH_3-12), 1.01 (m, 2H, CH_2-2′), 1.10-1.61 (m, 8H), 1.64 (s wide, 3H, CH_3-14), 1.79 (s, wide, 3H, CH_3-4), 1.90 (m, 1H, Ha-20), 1.94 (m, 1H, H-12), 2.25 (m, 2H, CH_2-16), 3.02 (dd, J = 7.5, 2.0 Hz, 1H, H-25), 3.40 (m, 1H, H-2), 3.57 (m, 1H, H-17), 3.75 (d, J = 7.4 Hz, 1H, H-13), 3.90 (d, J = 4.9 Hz, 1H, H-5), 4.07 (m, 1H, H-19), 4.23 (m, 2H, CH_2-1′), 4.48 (d, wide, J = 4.9 Hz, 1H, H-6), 4.63 (d wide, J = 2.0 Hz, 2H, CH_2-8a), 5.39 (m, 1H, H-3), 5.43 (m, 1H, H-15), 5.45 (m, 1H, H-11), 5.90 (t, J = 11.2 Hz, 1H, H-10), 6.22 (dt, J = 11.2, 2.0 Hz, 1H, H-9).

MS (CI, NH_3) : m/z 822 (MH^+ + 17), 804 (M^+), 669, 637, 619, 472, 345, 311.

Relay study : Opening-cyclization of avermectin macrolides

• *Preparation of naturally occurring aglycones*

The required B1a aglycone was prepared from commercial Ivermectin (generous gift from Merck, Sharp & Dohme) according to published procedures. The following steps were carried out : hydrolysis of the disaccharide moiety, which afforded a mixture containing 95% of 22,23-dihydroavermectin B1a aglycone and 5% B1b **1** aglycones in agreement with the original Ivermectin composition [34]; selective protection of this mixture at C5-OH; and final chromatographic separation, which gave silylated B1a aglycone **47** as well as 5% of the corresponding silylated B1b aglycone derivative **48** [35].

• *Aglycone opening, general procedure*

An oven-dried 5 mL flask was charged under nitrogen with the aglycone (0.1 mmol), the chosen alcohol or thiol (1-10 mmol) and titanium (IV) isopropoxide (0.1 mmol). The reaction mixture was heated to 100°C for 6-12 h, and after cooling to room temperature, it was diluted with light petroleum ether and poured over a pad of silica. Elution with light petroleum ether/diethyl ether mixtures (from 1:0 to 0:1) gave the required secoester as well as recovered aglycone.

• *{3E[2E,6E,4S,5S,(2R,4S,6S,8R(S),9S)], 3aS,4R,7R,7aR} Methyl 7-[(t-butyldimethylsilyl)oxy]-3a-hydroxy-3-{5-hydroxy-8-[4-hydroxy-9-methyl-8-(1-methylpropyl)-1,7-dioxaspiro[5.5]undecan-2-yl]-4,6-dimethylocta-2,6-dienylidene}-6-methyl-2,3,3a,4,7,7a-hexahydrobenzofuran-4-carboxylate* **49a**

5-O-TBS 22,23-Dihydroavermectin B1a aglycone **47** (105 mg, 0.15 mmol) and methanol (0.61 mL, 15 mmol) were treated as above to give pure **49a** (64 mg, 58% yield) and recovered aglycone **47** (22 mg, 21%yield).

49a : $[\alpha]_D$ = −8.2 (c = 2.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.10 (2s, 6H, $2CH_3$, $(CH_3)_2$-Si), 0.76 (d, J = 5.5 Hz, 3H, CH_3-26), 0.79 (d, J = 6.7 Hz, 3H, CH_3-24), 0.86 (t, J = 7.6 Hz, 3H, CH_3-27), 0.90 (s, 9H, $3CH_3$, $(CH_3)_3$C-Si), 1.00-1.35 (m, 7H), 1.50 (m, 6H), 1.61 (s, 3H, CH_3-14), 1.79 (s, wide, 3H, CH_3-4), 1.92 (m, 1H), 1.94 (m, 1H, H-12), 2.26 (m, 2H, CH_2-16), 2.28 (m, 1H), 3.12 (d, wide, J = 7.5 Hz, 1H, H-25), 3.45 (m, 1H, H-2), 3.59 (m, 1H, H-17), 3.68 (d, J = 8.5 Hz, 1H, H-13), 3.73 (s, 3H, $COOCH_3$), 3.91 (d, J = 4.8 Hz, 1H, H-5), 4.05 (m, 1H, H-19), 4.49 (m, 1H, H-6), 4.63 (d wide, J = 2.0 Hz, 2H, CH_2-8a), 5.40 (m, 1H, H-3), 5.43 (t, J = 7.5 Hz, 1H, H-15), 5.64 (dd, J = 14.5, 8.3 Hz, 1H, H-11), 5.95 (dd, J = 14.5, 11.2 Hz, 1H, H-10), 6.07 (dt, J = 11.2, 2.0 Hz, 1H, H-9).

^{13}C NMR ($CDCl_3$, 100,57 MHz), δ : −4.75 ($2CH_3$, $(CH_3)_2$-Si), 11.21 (CH_3-14), 11.52 (CH_3-27), 12.29 (CH_3-26), 16.89 (CH_3-24), 17.32 (CH_3-12), 18.12 (1C, $(CH_3)_3C$-Si),

19.75 (CH_3-4), 25.64 ($3CH_3$, $(CH_3)_3$C-Si), 27.23 (C-27), 27.94 (C-23), 31.10 (C-24), 33.91 (C-16), 35.30 (C-26), 35.65 (C-22), 40.42 (C-18), 41.11 (C-12), 44.89 (C-20), 46.49 (C-2), 52.14 ($COOCH_3$), 64.79 (C-19), 67.52 (C-17), 68.56 (C-8a), 69.14 (C-5), 76.85 (C-25), 78.24 (C-7), 81.53 and 83.06 (C-6 and C-13), 97.10 (C-21), 117.30 (C-3), 119.08 (C-9), 124.74 (C-15), 126.75 (C-10), 136.58 (C-14), 137.72 (C-4), 138.22 (C-11), 143.76 (C-8), 173.84 (C-1).

MS (CI, NH_3) : m/z 748, 731 ($M^+ - 1$), 713, 697, 681, 657, 639, 584, 565, 547, 406, 390, 333, 259.

MS (EI) : m/z 406, 390, 333, 307, 273, 238, 218, 199, 125, 95, 75.

• *{3E[2E,6E,4S,5S,(2R,4S,6S,8R(S),9S)], 3aS,4R,7R,7aR} Ethyl 7-[(t-Butyldimethylsilyl)oxy]-3a-hydroxy-3-{5-hydroxy-8-[4-hydroxy-9-methyl-8-(1-methylpropyl)-1,7-dioxaspiro[5.5]undecan-2-yl]-4,6-dimethylocta-2,6-dienylidene}-6-methyl-2,3,3a,4,7,7a-hexahydrobenzofuran-4-carboxylate* **49b**

From 35 mg (50 μmol) of 5-O-TBS 22,23-dihydroavermectin B1a aglycone **47** and 0.2 mL ethanol (3.4 mmol), were obtained 16.9 mg of pure **49b** (45%yield) and 6.2 mg of recovered **47** (18%).

49b : ^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.10 (2s, 6H, $(CH_3)_2$-Si), 0.75 (d, J = 5.6 Hz, 3H, CH_3-26), 0.78 (d, J = 6.7 Hz, 3H, CH_3-24), 0.88 (t, J = 7.3 Hz, 3H, CH_3-27), 0.90 (s, 9H, $(CH_3)_3$C-Si), 0.90 (d, J = 6 Hz, 3H, CH_3-12), 1.00-1.50 (m, 12H), 1.27 (t, J = 7.0 Hz, 3H, $COOCH_2CH_3$), 1.61 (s, 3H, CH_3-14), 1.78 (s, 3H, CH_3-4), 1.92 (m, 1H), 1.94 (m, 1H, H-12), 2.25 (m, 2H, CH_2-16), 3.12 (d, wide, J = 8.7 Hz, 1H, H-25), 3.41 (m, 1H, H-2), 3.59 (m, 1H, H-17), 3.68 (d, J = 8.7 Hz, 1H, H-13), 3.89 (d, J = 4.9 Hz, 1H, H-5), 4.05 (m, 1H, H-19), 4.19 (q, J = 7.0 Hz, 2H, $COOCH_2CH_3$), 4.49 (m, 1H, H-6), 4.62 (d, wide, J = 2.0 Hz, 1H, CH_2-8a), 5.40 (m, 1H, H-3), 5.43 (m, 1H, H-15), 5.65 (dd, J = 14.5, 8.4 Hz, 1H, H-11), 5.95 (dd, J = 14.5, 11.2 Hz, 1H, H-10), 6.06 (dt, J = 11.2, 2.0 Hz, 1H, H-9).

MS (CI, NH_3) : m/z 763 ($M^+ - 1 + 17$), 745 ($M^+ - 1$), 727 ($M^+ - 1 - 18$), 711, 671, 653, 579, 561, 404, 377, 325, 273.

MS (EI) : m/z 347, 333, 199, 159, 113, 95, 75, 58.

• *{3E[2E,6E,4S,5S,(2R,4S,6S,8R(S),9S)], 3aS,4R,7R,7aR} t-Butyl 7-[(t-butyldimethylsilyl)oxy]-3a-hydroxy-3-{5-hydroxy-8-[4-hydroxy-9-methyl-8-(1-methylpropyl)-1,7-dioxaspiro[5.5]undecan-2-yl]-4,6-dimethylocta-2,6-dienylidene}-6-methyl-2,3,3a,4,7,7a-hexahydrobenzofuran-4-carbothioate* **49e**

5-O-TBS B1a aglycone **47** (100 mg, 0.14 mmol) and *t*-butanethiol (1.28 g, 1.6 mL, 14.2 mmol) gave under the same conditions the expected thioester **49e** (21 mg, 20% yield) and recovered **47** (85 mg, 70%).

49e : ^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.10 (s, wide, 6H, 2 CH_3-Si), 0.75 (d, 3H, J = 5.0 Hz, CH_3-26), 0.77 (d, 3H, J = 7.0 Hz, CH_3-24), 0.86 (t, 3H, J = 7.2 Hz, CH_3-27), 0.90 (s, 9H, $3CH_3$, $(CH_3)_3$C-Si), 1.00-1.35 (m, 7H), 1.23 (s, 9H, $3CH_3$, $(CH_3)_3$C-S), 1.47 (m, 6H), 1.61 (s, 3H, CH_3-14), 1.77 (s, 3H, CH_3-4), 1.92 (m, 1H), 1.94 (m, 1H, H-12), 2.26 (m, 2H, H2-16), 2.28 (m, 1H), 3.10 (d, wide, 1H, J = 7.5 Hz, H-25), 3.34 (m, 1H, H-2), 3.57 (m, 1H, H-17), 3.66 (d, 1H, J = 8.8 Hz, H-13), 3.87 (d, 1H, J = 5.0 Hz, H-5), 4.04 (m, 1H, H-19), 4.46 (m, 1H, H-6), 4.61 (s, wide, 2H, H2-8a), 5.35 (m, 1H, H-3), 5.42 (t, 1H, J = 6.2 Hz, H-15), 5.61 (dd, 1H, J = 15.0, 8.8 Hz, H-11), 5.93 (dd, 1H, J = 15.0, 11.2 Hz, H-10), 6.04 (d, wide, 1H, J = 11.2 Hz, H-9).

MS (CI, NH_3) : 808 ($MH^+ + 17$), 794, 777, 757, 743, 725, 609, 593, 575, 418, 361, 325, 287, 235, 159.

• *{3E[2E,6E,4S,5S,(2R,4S,6S,8R(S),9S)], 3aS,4R,7R,7aR} Allyl 7-[(t-Butyldimethylsilyl)oxy]-3a-hydroxy-3-{5-hydroxy-8-[4-hydroxy-9-methyl-8-(1-methylpropyl)-1,7-dioxaspiro[5.5]undecan-2-yl]-4,6-dimethylocta-2,6-dienylidene}-6-methyl-2,3,3a,4,7,7a-hexahydrobenzofuran-4-carboxylate* **49f**

5-O-TBS 22,23-Dihydroavermectin B1a aglycone **47** (46 mg, 66 μmol) and allylic alcohol (372 mg, 448 μL, 6.57 mmol) were treated according to the general procedure to give the allyl ester **49f** (28 mg, 56% yield) as well as recovered aglycone **47** (16 mg, 34%). This product was unstable and prolonged standing under the reaction conditions led to decomposition.

49f : ^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.15 (s, wide, 6H, 2 CH_3-Si), 0.75 (d, 3H, J = 5.0 Hz, CH_3-26), 0.78 (d, 3H, J = 6.7 Hz, CH_3-24), 0.82 (t, 3H, J = 7.1 Hz, CH_3-27), 0.90 (s, 9H, 3 CH_3-C-Si), 1.00-1.35 (m, 8H), 1.47 (m, 9H), 1.61 (s, 3H, CH_3-14), 1.78 (s, wide, 3H, CH_3-4), 1.90 (m, 1H), 1.94 (m, 1H, H-12), 2.27 (m, 2H, H_2-16), 3.12 (d, wide, J = 7.5 Hz, 1H, H-25), 3.45 (m, 1H, H-2), 3.59 (m, 1H, H-17), 3.69 (d, J = 8.5 Hz, 1H, H-13), 3.91 (d, J = 4.8 Hz, 1H, H-5), 4.05 (m, 1H, H-19), 4.48 (m, 1H, H-6), 4.60 (m, 2H, CH_2-1′), 4.62 (d wide, J = 2.0 Hz, 2H, H_2-8a), 5.25 (d wide, J = 11.5 Hz, 1H, Hb-3′), 5.30 (m, 1H, H-3), 5.31 (d wide, J = 18.1 Hz, 1H, Ha-3′), 5.35 (t, J = 7.0 Hz, 1H, H-15), 5.63 (dd, J = 14.3, 8.4 Hz, 1H, H-11), 5.90 (m, 1H, H-2′), 5.94 (dd, J = 14.3, 10.9 Hz, 1H, H-10), 6.06 (dt, J = 10.9, 2.0 Hz, 1H, H-9).

MS (CI, NH_3) : 774 ($M^+ - 1 + NH_3$), 757 ($M^+ - 1$), 739, 723, 607, 591, 573, 325, 285.

• *{3E[2E,6E,4S,5S,(2R,4S,6S,8R(S),9S)], 3aS,4R,7R,7aR} [2-(Trimethylsilyl)ethyl] 7-[(t-Butyldimethylsilyl)oxy]-3a-hydroxy-3-{5-hydroxy-8-[4-hydroxy-9-methyl-8-(1-methylpropyl)-1,7-dioxaspiro[5.5]undecan-2-yl]-4,6-dimethylocta-2,6-dienylidene}-6-methyl-2,3,3a,4,7,7a-hexahydrobenzofuran-4-carboxylate* **49g**

Under the usual conditions 5-O-TBS B1a aglycone **47** (110 mg, 0.16 mmol) and 2-(trimethylsilyl)ethanol (300 μL, 2.1 mmol) gave the TSE-secoester **49g** (69 mg, 61% yield) and aglycone **47** (24 mg, 22%).

49g : $[\alpha]_D = -6.9$ (c = 1.7, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.03 (s, 9H, $(CH_3)_3$-Si), 0.10 and 0.11 (2s, 6H, $2CH_3$, $(CH_3)_2$-Si), 0.75 (d, J = 5.7 Hz, 3H, CH_3-26), 0.79 (d, J = 6.7 Hz, 3H, CH_3-24), 0.87 (t, J = 7.4 Hz, 3H, CH_3-27), 0.90 (s, 9H, $3CH_3$, $(CH_3)_3$C-Si), 1.01 (m, 2H, CH_2-2′), 1.07-1.37 (m, 6H), 1.48 (m, 8H), 1.61 (s, 3H, CH_3-14), 1.78 (s, wide, 3H, CH_3-4), 1.93 (m, 1H), 1.94 (m, 1H, H-12), 2.28 (m, 2H, CH_2-16), 3.12 (d, wide, J = 10.0 Hz, 1H, H-25), 3.39 (m, 1H, H-2), 3.56 (m, 1H, H-17), 3.68 (d, J = 8.6 Hz, 1H, H-13), 3.90 (d, J = 4.9 Hz, 1H, H-5), 4.08 (m, 1H, H-19), 4.22 (m, 2H, CH_2-1′), 4.47 (m, 1H, H-6), 4.63 (d, wide, 2H, J = 1.9 Hz, CH_2-8a), 5.39 (m, 1H, H-3), 5.44 (t, J = 7.0 Hz, 1H, H-15), 5.63 (dd, J = 14.4, 8.0 Hz, 1H, H-11), 5.95 (dd, J = 14.4, 11.2 Hz, 1H, H-10), 6.07 (dt, J = 11.2, 1.9 Hz, 1H, H-9).

^{13}C NMR ($CDCl_3$, 100,57 MHz), δ : −4.93 and −4.60 ($2CH_3$, $(CH_3)_2$-Si), 1.55 ($3CH_3$, $(CH_3)_3$-Si), 11.30 (CH_3-14), 11.68 (CH_3-27), 12.45 (CH_3-26), 17.09 (CH_3-24), 17.25 (C-2′), 17.48 (CH_3-12), 18.29 (1C, $(CH_3)_3C$-Si), 19.90 (CH_3-4), 25.80 ($3CH_3$, $(CH_3)_3$C-Si), 27.38 (C-27), 28.09 (C-23), 31.25 (C-24), 34.08 (C-16), 35.45 (C-26),

35.80 (C-22), 40.60 (C-18), 41.33 (C-12), 45.02 (C-20), 46.55 (C-2), 63.83 (C-1'), 64.96 (C-19), 67.67 (C-17), 68.69 (C-8a), 69.30 (C-5), 77.02 (C-25), 78.47 (C-7), 81.75 and 83.02 (C-6 and C-13), 97.26 (C-21), 117.59 (C-3), 119.14 (C-9), 125.04 (C-15), 127.03 (C-10), 136.67 (C-14), 137.73 (C-4), 138.23 (C-11), 144.07 (C-8), 173.93 (C-1).

MS (CI, NH_3) : m/z 817, 731, 713, 699, 683, 508, 492, 475, 325, 285.

• *Secoacid preparation (Relay synthesis) {3E/2E,6E,4S,5S,(2R,4S,6S,8R(S),9S)}, 3aS,4R,7R,7aR} 7-[(t-Butyldimethylsilyl)oxy]-3a-hydroxy-3-{5-hydroxy-8-[4-hydroxy-9-methyl-8-(1-methylpropyl)-1,7-dioxaspiro[5.5]undecan-2-yl]-4,6-dimethylocta-2,6-dienylidene}-6-methyl-2,3,3a,6,7,7a-hexahydrobenzofuran-4-carboxylic acid* **50**

■ *From TES secoester* **49g**

The deprotection reaction was carried out according to the procedure of Gerlach *et al* [38].

To a solution of 2-(trimethylsilyl)ethyl secoester **49g** (10 mg, 12 μmol) in THF (100 μL) under nitrogen was added a solution of *p*-toluenesulfonic acid monohydrate (PTSA, 4.6 mg, 24 μmol) and nBu$_4$NF (18.8 mg, 72 μmol) in THF (400 μL). The reaction mixture was stirred for 12 h at room temperature, diluted with ethyl acetate (2.5 mL), washed with water (5 × 1 mL) and dried over $MgSO_4$. Evaporation under reduced pressure gave the desired secoacid **50** (9 mg, quantitative).

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.10 (s, wide, 6H, 2CH_3, $(CH_3)_2$-Si), 0.75 (d, J = 5.0 Hz, 3H, CH_3-26), 0.78 (d, J = 7.0 Hz, 3H, CH_3-24), 0.88 (t, J = 7.5 Hz, 3H, CH_3-27), 0.90 (s, 9H, 3CH_3, $(CH_3)_3$C-Si), 1.02 (d, J = 6.2 Hz, 3H, CH_3-12), 1.05-1.30 (m, 6H), 1.48 (m, 4H), 1.60 (s, 3H, CH_3-14), 1.78 (s, wide, 3H, CH_3-4), 1.92 (m, 1H), 1.95 (m, 1H, H-12), 2.26 (m, 2H, CH_2-16), 2.44 (m, 1H), 3.10 (d, wide, J = 7.5 Hz, 3H, H-25), 3.43 (m, 1H, H-2), 3.59 (m, 1H, H-17), 3.83 (d, J = 6.5 Hz, 1H, H-13), 3.87 (d, J = 4.5 Hz, 1H, H-5), 4.10 (m, 1H, H-19), 4.42 (m, 1H, H-6), 4.62 (s wide, 2H, CH_2-8a), 5.33 (t, J = 7.5 Hz, 1H, H-15), 5.42 (m, 1H, H-3), 5.60 (dd, J = 15.0, 8.0 Hz, 1H, H-11), 5.86 (dd, J = 15.0, 12.5 Hz, 1H, H-10), 6.07 (dt, J = 12.5, 2.0 Hz, 1H, H-9).

For further analytical purposes, this acid (9 mg) was treated with diazomethane in diethyl ether and purified by chromatography on silica to give the pure corresponding methyl secoester **49a** (9 mg, > 95% yield) which exhibited spectroscopic data identical to those of the product prepared from ring-opening of 5-OTBS 22,23-dihydroavermectin B1a aglycone **47**.

■ *From allyl secoester* **49f**

This reaction was carried out according to the procedure of Tsuji and Yamakawa [37]. The allyl secoester **49f** (20 mg, 26 μmol) dissolved in dioxane (180 μL) under argon was treated with ammonium formate (6.6 mg, 105 μmol), then bis-(triphenylphosphine) palladium(II) chloride (2.0 mg, 2.8 μmol). The reaction mixture was warmed to 100°C for 15 min and, after cooling down to room temperature, added with an aqueous formate/formic acid buffer (pH = 3, 1 mL). This mixture was extracted with ethyl acetate (3 × 0.5 mL), the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure to give crude secoacid **50** (25 mg, > 90% yield) which was used in the next step without further purification.

The spectroscopic data proved this product to be identical with the acid obtained above.

• *Macrolactonization : 5-OTBS 22,23-dihydroavermectin B1a aglycone* **47**

This reaction was carried out according to the procedure of Yonemitsu *et al* [40]. The crude secoacid **50** (20 mg, 28 μmol) was dissolved in xylene (2.5 mL) under argon. Triethylamine (6.0 μL, 43 μmol) and 4-(dimethylamino)pyridine (7 mg, 57 μmol) were added. To this mixture was introduced 2,4,6-trichlorobenzoyl chloride (6.4 μL, 40 μmol). The reaction mixture became cloudy. After stirring for 15 min at room temperature, diethyl ether was added and the mixture was filtered over a pad of celite. After evaporation of the filtrate under reduced pressure and purification by preparative TLC (diethyl ether/petroleum ether), pure aglycone **47** (6.0 mg, 30% yield for two steps from **49f** or **49g**) was obtained. $[\alpha]_D$ = +89° (c = 2.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 250 MHz), δ : 0.10 (s, wide, 6H, 2CH_3, $(CH_3)_2$-Si), 0.76 (d, J = 6.0 Hz, 3H, CH_3-26), 0.82 (d, J = 7.0 Hz, 3H, CH_3-24), 0.92 (t, J = 7.0 Hz, 3H, CH_3-27), 0.92 (s, 9H, 3CH_3, $(CH_3)_3$C-Si), 1.14 (d, J = 7.0 Hz, 3H, CH_3-12), 1.20-1.80 (m, 12H), 1.50 (s, 3H, CH_3-14), 1.75 (s, wide, 3H, CH_3-4), 1.97 (ddd, J = 11.9, 5.0, 2.5 Hz, 1H, Heq-20), 2.24 (m, 2H, CH_2-16), 2.49 (m, 1H, H-12), 3.12 (d, wide, J = 8.1 Hz, 1H, H-25), 3.31 (d, J = 2.5 Hz, 1H, H-2), 3.65 (m, 1H, H-17), 3.78 (d, J = 5.5 Hz, 1H, H-13), 3.96 (s, wide, 1H, H-5), 4.40 (m, 1H, H-6), 4.53 (d, wide, J = 15.2 Hz, 1H, Ha-8a), 4.63 (d, wide, J = 15.2 Hz, 1H, Hb-8a), 5.25-5.28 (m, 3H, H-3, H-15, H-19), 5.60 (m, 3H, H-9, H-10 and H-11).

^{13}C NMR ($CDCl_3$, 100.57 MHz), δ : −4.92 and −4.62 (2CH_3, $(CH_3)_2$-Si), 11.69 (CH_3-27), 12.49 (CH_3-26), 14.59 (CH_3-14), 17.40 (CH_3-24), 18.35 (1C, $(CH_3)_3C$-Si), 19.19 (CH_3-12), 19.97 (CH_3-4), 25.82 (3CH_3, $(CH_3)_3$C-Si), 27.41 (C-27), 28.02 (C-23), 31.18 (C-24), 34.19 (C-16), 35.45 (C-26), 35.72 (C-22), 36.59 (C-18), 39.90 (C-12), 41.28 (C-20), 46.69 (C-2), 67.19 (C-17), 67.86 (C-8a), 68.60 (C-19), 69.38 (C-5), 77.32 (C-25 or C-6), 77.55 (C-6 or C-25), 80.03 (C-7), 80.10 (C-13), 97.39 (C-21), 117.08 and 117.35 (C-3 and C-15), 119.35 (C-9), 124.74 (C-10), 136.51 (C-11), 137.23 (C-4), 138.65 (C-14), 140.19 (C-8), 173.70 (C-1).

MS (CI, NH_3) : m/z 718 (MH^+ + 17), 701 (MH^+), 683 (MH^+ − 18), 569, 551, 307, 207, 195.

All these data are identical to those obtained for the product directly prepared from commercial Ivermectin.

Total synthesis of 22,23-dihydroavermectin B1b aglycone **1**

• *5-OTBS 22,23-dihydroavermectin B1b aglycone* **48**

The synthetic secoester **46** (15 mg, 21 μmol) was treated with an aqueous solution of TBAF-TsOH according to Gerlach's procedure (already used above for the deprotection of 5-OTBS 2-(trimethylsilyl)ethyl B1a secoester **49g**). This reaction delivered the crude B1b secoacid **51** which was then treated with the same macrolactonization conditions as its B1a homologue (see above) except that toluene (21 mL) was used as solvent to give, after silica-gel MPLC purification, pure aglycone **48** (4.4 mg, 30% yield for two steps from 5-OTBS secoester **46**). $[\alpha]_D$ = +104 (c = 1.8, $CHCl_3$).

^{1}H NMR (400 MHz), δ : 0.12 (s, wide, 6H, 2CH_3, $(CH_3)_2$-Si), 0.77 (d, J = 6.2 Hz, 3H, CH_3-26), 0.83 (d, J = 6.8 Hz, 3H, CH_3-26), 0.90 (s, 9H, 3CH_3, $(CH_3)_3$C-Si), 1.01 (d, J = 7.0 Hz, 3H, CH_3-24), 1.12 (d, J = 7.0 Hz, 3H, CH_3-12), 1.20-1.50 (m, 5H), 1.46 (s, 3H, CH_3-14), 1.48-1.80 (m, 3H), 1.75 (s, 3H, CH_3-4), 1.85 (qd, J = 7.5, 1.8 Hz, 1H), 1.97 (ddd, J = 12.0, 5.0, 1.5 Hz, 1H, Heq-20), 2.27 (dd, J = 12.0, 11.0 Hz, 1H, Ha-16), 2.30 (dd, J = 11.0, 6.0 Hz, 1H, Hb-16), 2.47 (m, 1H, H-12), 3.03 (dd, J = 9.5, 2.0 Hz, 1H, H-25), 3.28 (m, J = 2.5 Hz, 1H, H-2), 3.65

(m, 1H, H-17), 3.77 (d, J = 5.5 Hz, 1H, H-13), 3.96 (s wide, 1H, H-5), 4.08 (s, wide, 1H, OH), 4.40 (s wide, 1H, H-6), 4.53 (dd, J = 14.2, 1.5 Hz, 1H, Ha-8a), 4.65 (dd, J = 14.2, 1.5 Hz, 1H, Hb-8a), 5.32 (m, 3H, H-3, H-15, H-19), 5.32 (m, 1H, H-3), 5.68 (m, 1H, H-10), 5.72 (m, 1H, H-11), 5.76 (dt, J = 10.0, 1.5 Hz, 1H, H-9).

^{13}C NMR ($CDCl_3$, 100,57 MHz), δ : −4.88 and −4.62 ($2CH_3$, $(CH_3)_2$-Si), 14.15 (CH_3-26), 14.63 (CH_3-14), 17.34 (CH_3-24), 18.20 (1C, $(CH_3)_3C$-Si), 19.20 (CH_3-12), 20.00 (CH_3-4), 21.03 (CH_3-26), 25.85 ($3CH_3$, $(CH_3)_3C$-Si), 28.03 (C-23), 31.18 (C-26), 31.55 (C-24), 34.27 (C-16), 35.67 (C-22), 36.72 (C-18), 39.95 (C-12), 41.28 (C-20), 45.71 (C-2), 67.20, 68.59 and 69.43 (C-5, C-17 and C-19), 67.92 (C-8a), 77.64 (C-6 or C-13), 78.33 (C-25), 80.04 (C-7), 80.08 (C-13 or C-6), 97.42 (C-21), 117.16 and 117.35 (C-3 and C-15), 119.30 (C-9), 124.81 (C-10), 136.46 (C-11), 137.29 (C-4), 138.65 (C-14), 140.34 (C-8), 173.80 (C-1).

MS (CI, NH_3) : m/z 704 (MH^+ + 17), 687 (MH^+), 686 (M^+), 669 (MH^+ − 18), 555, 537, 509, 293.

All these data are identical to those obtained for the same product directly prepared from commercial Ivermectin.

• *22,23-Dihydroavermectin B1b aglycone* **1**

The removal of the TBS protecting group of **48** was carried out according to the procedure of Mrozik [35].

Silyl ether **48** (4 mg, 5.8 μmol) was treated with a 1% methanolic solution of TsOH · H_2O (460 μL, 23.2 μmol) at room temperature. After stirring for 20 min, the reaction mixture was diluted with ethyl acetate and washed with dilute aqueous sodium bicarbonate solution, and then with brine. After decantation, the organic phase was dried over magnesium sulfate, filtered over celite and concentrated under reduced pressure. Purification of the crude product by silica micro-column chromatography (light petroleum ether/diethyl ether from 4:1 to 0:1) gave pure aglycone **1** (1.9 mg, 58% yield). $[\alpha]_D$ = +138 (c = 0.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz), δ : 0.82 (d, J = 6.0 Hz, 3H, CH_3-26), 0.89 (d, J = 7.0 Hz, 3H, CH_3-26), 1.08 (d, J = 7.0 Hz, 3H, CH_3-24), 1.20 (d, J = 7.0 Hz, 3H, CH_3-12), 1.38 (t, J = 12.0 Hz, 1H, Hax-20), 1.52 (m, 6H), 1.55 (s, 3H, CH_3-14), 1.69 (d wide, J = 12.5 Hz, 1H), 1.79 (d wide, J = 13.0 Hz, 1H), 1.90 (s, wide, 3H, CH_3-4), 1.93 (qd, J = 6.5, 2.0 Hz, 1H, Heq-18), 2.02 (ddd, J = 12.0, 5.0, 1.5 Hz, 1H, Heq-20), 2.30 (dd, J = 13.0, 11.0 Hz, 1H, Ha-16), 2.36 (m, 1H, Hb-16), 2.55 (m, 1H, H-12), 3.11 (dd, J = 10.0, 2.0 Hz, 1H, H-25), 3.29 (dd, J = 5.0, 2.5 Hz, 1H, H-2), 3.72 (m, 1H, H-17), 4.00 (d, J = 6.5 Hz, 1H, H-5), 4.04 (s, wide, 1H, OH-7), 4.12 (m, 1H, H-13), 4.32 (d, J = 6.5 Hz, 1H, H-6), 4.68 (dd, J = 14.0, 2.0 Hz, 1H, Ha-8a), 4.74 (dd, J = 14.0, 2.0 Hz, 1H, Hb-8a), 5.39 (m, 2H, H-15, H-19), 5.45 (s, wide, 1H, H-3), 5.72 (dd, J = 14.0, 10.0 Hz, 1H, H-10), 5.80 (d, J = 14.0 Hz, 1H, H-11), 5.85 (dt, J = 10.0, 2.0 Hz, 1H, H-9).

^{13}C NMR ($CDCl_3$, 100.57 MHz). δ : 14.15 (CH_3-26), 14.59 (CH_3-14), 17.35 (CH_3-24), 19.13 (CH_3-12), 19.93 (CH_3-4), 21.05 (CH_3-26), 28.02 (C-23), 28.29 (C-26), 31.57 (C-24), 36.25 (C-16), 35.69 (C-22), 36.91 (C-18), 40.06 (C-12), 41.28 (C-20), 45.65 (C-2), 67.21 and 67.71 (C-5 and C-17), 68.47 (C-8a), 68.49 (C-19), 77.68, 78.38 (C-25), 79.09 (C-13 or C-6), 80.20 (C-7), 97.42 (C-21), 117.13 and 117.21 (C-3 and C-15), 119.35 (C-9), 124.75 (C-10), 136.98 (C-11), 137.72 (C-4), 138.59 (C-14), 139.81 (C-8), 173.57 (C-1).

MS (CI, NH_3) : m/z 590 (MH^+ + 17), 573 (MH^+), 555 (MH^+ − 18), 537, 293, 181, 151, 137.

All data are identical to those of the product obtained from commercial Ivermectin.

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