Hyrtiosanes from Labdanes: (–)-Hyrtiosal from Sclareol

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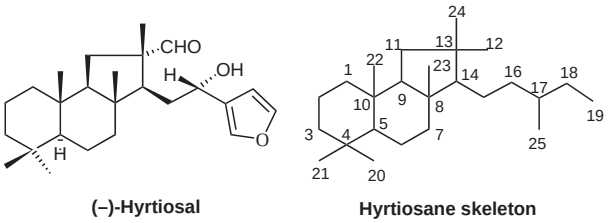
Abstract: (–)-Hyrtiosal and its C-16 epimer have been prepared from sclareol in moderate yield. The absolute configuration of natural product (–)-hyrtiosal has being determined.

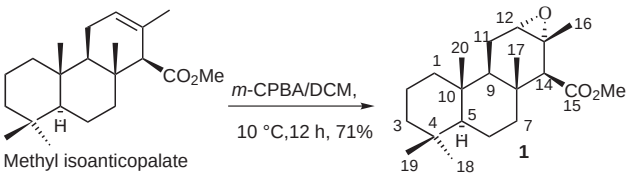
Key words: terpenoids, labdanes, hyrtiosal, sclareol, natural products, coupling, antitumor agents

Hyrtiosal, a new sesterterpenoid possessing a novel arrangement of a tricarbocyclic skeleton of unknown absolute stereochemistry was isolated[1] from the okinawan marine sponge *Hyrtios erectus*. This compound inhibited the proliferation of KB cells *in vitro*. Hyrtiosal possesses a new carbon skeleton that was called hyrtiosane (Figure). Recently, we reported the synthesis and absolute configuration of hyrtiosal.[2]



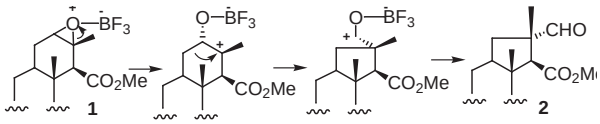
Figure

According to the biosynthetic model for hyrtiosal proposed by Iguchi et al[1] from a cheilanthane skeleton, our synthetic strategy starts from epoxide **1**, itself synthesized from methyl isoanticopalate obtained from sclareol[3] (Scheme 1). This constitutes a new route to compounds with the hyrtiosane skeleton from a compound with a labdane skeleton (sclareol).



Scheme 1

In the synthesis of *ent*-cheilanthenediol Heissler et al.[4] described the rearrangement of an epoxide on a tricyclic skeleton to an *ent*-hyrtiosal derivative using lithium diisobutyl-*n*-butylaluminium hydride in refluxing toluene. In our case the rearrangement of **1** was done with $BF_3{\cdot}Et_2O$ to give aldehyde **2** in 96% yield by the mechanism shown in Scheme 2. The absolute configuration of **2** was confirmed by X-ray analysis of its derivative **5**, as will be shown later.



Scheme 2

The synthesis of sesterterpene hyrtiosal was planned via the introduction of a furan ring to aldehyde **8** (Scheme 3). Therefore, at the outset, homologation of compound **2** was required.

Before the homologation was attempted it was necessary to protect the aldehyde functionality in **2** using a dithioacetal, and in turn to transform the methyl ester into an aldehyde.

As shown in Scheme 3 the following reactions were carried out. Treatment of **2** with ethylendithiol led to compound **3**. Reduction of **3** to the aldehyde did not take place in one step; it was necessary to use DIBALH reduction to give alcohol **4** in an excellent 94% yield. The subsequent oxidation of **4** to give **5** could be done either with CrO_3 in pyridine[5] or by tetrapropylammonium perruthenate (TPAP) oxidation.[6] The first oxidation gave 61% yield of the required aldehyde **5** and 11% of a mixture 1:1 of sulfoxides **6a**,**b**. In the second oxidation, the yield to aldehyde **5** dropped to 45%, and the sulfoxides were obtained in 27% yield.

Aldehyde **5** was crystallized in hexane–benzene and its absolute configuration was determined by X-ray analysis,[7] confirming its stereochemistry, as well as that of aldehyde **2**.

Treatment of aldehyde **5** with (methoxymethyl)triphenylphosphonium chloride using NaHMDS as base[8] led to a 1:4 mixture of inseparable enol ethers **7a**,**b** in a 92% yield. Treatment of **7a**,**b** with *p*-TsOH gave the homologated aldehyde **8** in a 98% yield.

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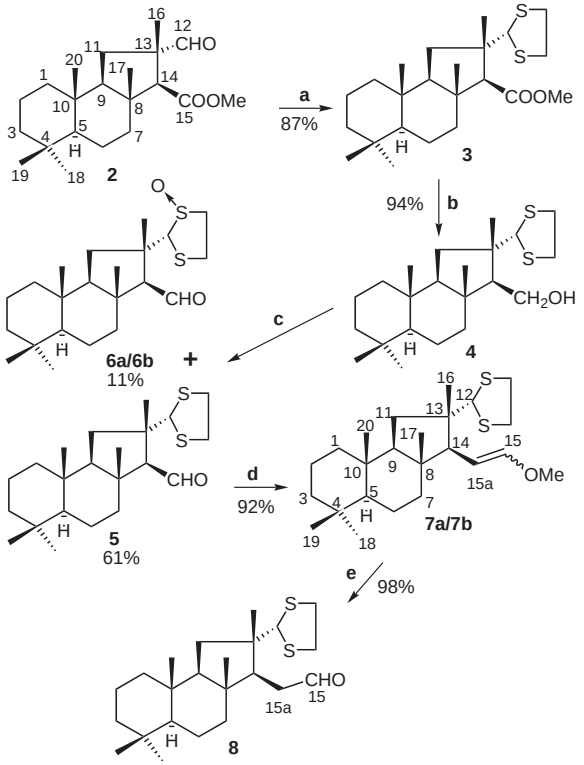
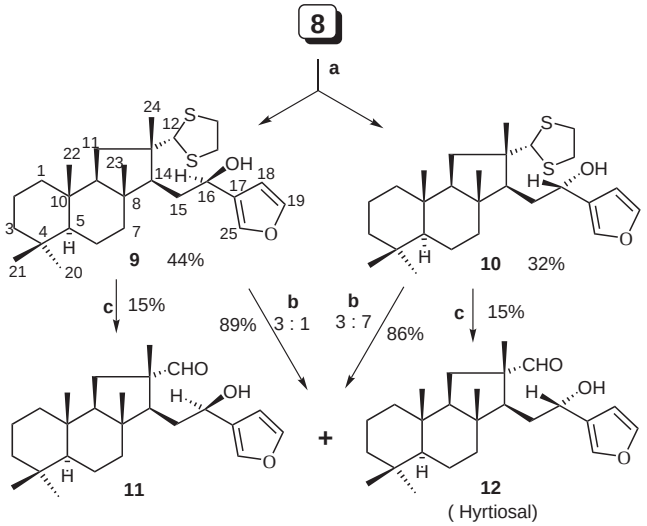


Scheme 3 a) Ethanedithiol, DCM, r.t.; b) DIBAL, DCM, –78 ºC, 1 h.; c) CrO_3, pyridine, r.t., 0.25 h [or TPAP, *N*-methylmorpholine *N*-oxide (NMO), DCM, r.t.; **5**: 45%, **6a**,**b**: 27%]; d) Ph_3P=CHOMe, NaHMDS, THF, –78 ºC, 1 h.; e) acetone, *p*-TsOH, r.t.

Once obtained it was necessary to couple aldehyde **8** with an organometallic species. In this regard, 3-lithiofuran was chosen due to its reactivity towards aldehydes. Generation of the organometallic reagent was done by treatment of 3-bromofuran with BuLi. This was then reacted with aldehyde **8** to give a 4:3 mixture of furano derivatives **9** and **10** (Scheme 4) that were separated by column chromatography. The stereochemistry of both compounds was determined later on.

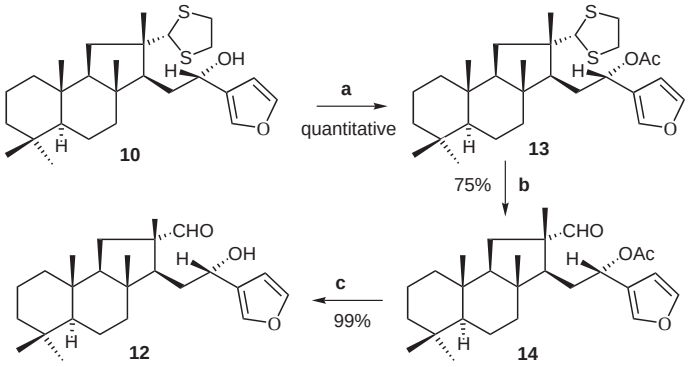
For the deprotection of the aldehyde different reagents were tested. Treatment of **9** with $Hg(ClO_4)_2$[9] gave a 3:1 mixture of **11** and **12** in 89% yield, that were separated by column chromatography. Treatment of **10** in the same conditions gave a 3:7 mixture of **11** and **12** in 86% yield. However, when the deprotection of **9** and **10** was carried out with [bis(trifluoroacetoxy)iodo]benzene,[10] there was no epimerization but the yield dropped to 15% in both cases.



Scheme 4 a) BuLi, 3-bromofuran, THF, –78 ºC, 1 h.; b) $Hg(ClO_4)_2$, $CaCO_3$, THF, H_2O, r.t., 10 min.; c) $PhI(O_2CCF_3)_2$, MeOH–H_2O 99:1, r.t., 10 min.

In order to assure no epimerization at C-16 during deprotection whilst keeping high yields, acetylation of the hydroxy group was planned Scheme 5. Acetylation of compound **10** with Ac_2O–pyridine gave **13**, in quantitative yield. After treatment with $Hg(ClO_4)_2$ this led to aldehyde **14** in 75% yield. This compound was transformed under basic conditions into aldehyde **12.** The physical properties of compound **12** were identical to those of (–)-hyrtiosal. As the stereochemistry of (–)-hyrtiosal has been determined by Iguchi et al.[1] by two dimensional NOESY experiments, corroborated by our NOE studies, the stereochemistry of **10** is established as the one of compound **9** shown in Scheme 4.

The same reaction sequence, as described in Scheme 5 has been followed with the other alcohol **9** giving **15**, **16** and **11** epimers on C-16 of **13**, **14** and **12**, respectively.



Scheme 5 a) Ac_2O, pyridine, r.t.; b) $Hg(ClO_4)_2$,$CaCO_3$, THF, H_2O, r.t., 0.1 h.; c) K_2CO_3, MeOH (2%), r.t., 2 h.

The antitumor activity of the compounds **11** and **12** was evaluated in a number of human tumor cell lines by measuring the metabolic activity of viable cells by the XTT assay. The following cell lines were examined: HL-60 (human acute leukemia), HeLa (human cervix carcinoma), HT-29 (human colon carcinoma), and A549 (human lung carcinoma). Both compounds exert an antiproliferative effect on human tumor cells, derived from leukemia and solid tumors, with an IC_{50} value ranging between 2.4 and 16.2 μM. Both compounds have similar IC_{50} values against a number of human tumor cell lines, suggesting a similar antineoplastic activity. Leukemic cells seem to be slightly more sensitive to the antiproliferative action of both compounds. Within solid tumor cell lines, HeLa cells were slightly more sensitive to the action of **12** and **11**, suggesting a certain higher sensitivity of cervix carcinoma to the antiproliferative action of these compounds. Compound **11** showed a slightly higher antineoplastic activity against HeLa cells than **12**.

In this paper a simple route for the synthesis of (–)-hyrtiosal from methyl isoanticopalate has been described, having stated the absolute configuration. This methodology paves the way for the transformation of labdanes to hyrtiosanes.

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. Mps were determined with a Kofler hot stage mp apparatus and are uncorrected. IR spectra were recorded on a BOMEM 100 FT IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ = 7.26 and δ = 77.0 for ^{1}H and ^{13}C, respectively, using a Bruker WP-200 SY and a Bruker DRX 400 MHz. Chemical shifts are reported in δ, ppm and coupling constants (*J*) are given in Hz. MS were performed in a VG-TS 250 spectrometer at 70 eV ionizing voltage. Mass spectra are presented as *m*/*z* (% rel. int.). HRMS were recorded in a VG Platform spectrometer using electronic impact (EI) or fast atom bombardment (FAB) technique. Optical rotations were determined in a Perkin-Elmer 241 polarimeter in 1 dm cells. Et_2O, THF and benzene were distilled from sodium, and pyridine and CH_2Cl_2 were distilled under argon from CaH_2.

Methyl 12α,13α-Epoxyisoanticopal-15-oate (1)

To an ice cooled solution of methyl isoanticopalate (7.0 g, 22.3 mmol) in anhyd CH_2Cl_2 (500 mL), was added MCPBA (7.0 g, 40.6 mmol) and the flask was stoppered with a drying tube containing $CaCl_2$. After being stirred for 12 h, the solution was diluted with Et_2O (600 mL) and washed successively with aq Na_2SO_3 (10%, 3 × 100 mL), aq $NaHCO_3$ (6%, 3 × 100 mL) and H_2O (3 × 100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane–EtOAc, 95:5) to give **1**.

Yield: 5.3 g (71%); colorless solid; mp 155–157 °C (crystals were obtained from hexane–Et_2O); $[\alpha]_D^{20}$ –23.0 (*c* 0.85, $CHCl_3$).

IR (neat): 1740, 1450, 1320, 1200, 1170, 1110, 1010 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.67 (3 H, s, CO_2Me), 3.05 (1 H, br s, H-12), 2.47 (1 H, s, H-14), 2.02 (1 H, dd, *J* = 14.8, 4.8, H-11_A), 1.80–1.68 (2 H, m), 1.65–1.42 (4 H, m), 1.35–1.13 (4 H, m), 1.29 (3 H, s, Me-16), 1.07 (3 H, s, Me-17), 0.97 (1 H, dd, *J* = 12.4, 4.8, H-9), 0.97–0.80 (2 H, m), 0.89 (3 H, s, Me-20), 0.83 (3 H, s, Me-18), 0.80 (3 H, s, Me-19).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.6 (C-15), 62.1 (C-12), 60.3 (C-14), 56.9 (C-13), 56.4 (C-5), 51.0 (CO_2Me), 50.3 (C-9), 41.9 (C-3), 40.4 (C-7), 39.5 (C-1), 37.3 (C-10), 36.1 (C-8), 33.5 (C-18), 33.1 (C-4), 21.8 (C-11), 21.7 (C-19), 22.4 (C-16), 18.4 (C-2, C-6), 15.8 (C-17), 15.1 (C-20).

EIMS: *m*/*z* (%) = 334 $(M)^+$ (36), 319 (80), 301 (71), 205 (53), 191 (64), 177 (91), 143 (73), 123 (68), 95 (75), 81 (100), 69 (80).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{34}O_3$ $(M)^+$: 334.2508; found: 334.2511.

Methyl 13*S*-11(12→13)-*abeo*-12-Oxoisoanticopal-15-oate (2)

To a stirred solution of **1** (367.1 mg, 1.1 mmol) in anhyd benzene (8 mL) at 0 °C, was added $BF_3{\cdot}Et_2O$ (5 mL) under argon. The mixture was heated up to 60 °C over 1 h and was poured into H_2O (8 mL). This solution was removed by extraction with Et_2O (3 × 100 mL). The organic layer was washed with aq $NaHCO_3$ (10%, 3 × 25 mL) and H_2O (3 × 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give **2**.

Yield: 356 mg (96%); colorless solid; $[\alpha]_D^{20}$ –10.3 (*c* 0.94, $CHCl_3$).

IR (neat): 2850, 1740, 1730, 1450, 1390, 1190 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.46 (1 H, s, H-12), 3.62 (3 H, s, CO_2Me), 2.80 (1 H, s, H-14), 2.03 (1 H, dt, *J* = 12.0, 3.2, H-7_A), 1.94 (1 H, dd, *J* = 12.0, 5.6, H-11_A), 1.65–1.37 (9 H, m), 1.35 (3 H, s, Me-16), 1.32–0.90 (3 H, m), 1.12 (3 H, s, Me-18), 0.88 (3 H, s, Me-17), 0.85 (3 H, s, Me-19), 0.82 (3 H, s, Me-20).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.7 (C-12), 171.6 (C-15), 59.9 (C-14), 57.7 (C-9), 57.1 (C-5), 52.6 (C-13), 50.9 (CO_2Me), 45.1 (C-8), 42,3 (C-3), 40.5 (C-7), 40.0 (C-1), 36.8 (C-10), 33.4 (C-18), 33.0 (C-11), 32.9 (C-4), 21.2 (C-19), 18.9 (C-2), 20.6 (C-16), 18.1 (C-6), 16.7 (C-17), 15.7 (C-20).

FABMS: *m*/*z* (%) = 335 $(M + H)^+$ (8), 303 (24), 245 (6), 191 (10), 154 (100), 107 (51), 69 (78).

HRMS (FAB): *m*/*z* calcd for $C_{21}H_{35}O_3$ $(M + H)^+$: 335.2585; found: 335.2583.

Methyl 13*S*-11(12→13)-*abeo*-12-Ethylenedithiaisoanticopal-15-oate (3)

To a solution of **2** (367 mg, 1.1 mmol) in anhyd CH_2Cl_2 (8 mL) was added 1,2-ethanedithiol (0.14 mL, 1.65 mmol) and $BF_3{\cdot}Et_2O$ (0.03 mL) under argon. After the solution was stirred for 12 h at r.t., aq $NaHCO_3$ (10%, 5 mL) was added and the aq layer was extracted with Et_2O (3 × 100 mL). The organic layer was washed with brine (3 × 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (hexane–EtOAc, 95:5) provided **3**.

Yield: 393.7 mg (87%); colorless oil; $[\alpha]_D^{20}$ –12.7 (*c* 0.6, $CHCl_3$).

IR (neat): 2930, 1736, 1458, 1433, 1389, 1159 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.85 (1 H, s, H-12), 3.62 (3 H, s, CO_2Me), 3.32–3.10 (4 H, m, SCH_2CH_2S), 2.47 (1 H, s, H-14), 1.80 (1 H, dt, *J* = 12.0, 3.2, H-7_A), 1.73 (1 H, dt, *J* = 12.0, 5.6, H-11_A), 1.68–1.37 (8 H, m), 1.39 (3 H, s, Me-16), 1.36–0.88 (4 H, m), 1.01 (3 H, s, Me-18), 0.86 (3 H, s, Me-17), 0.84 (3 H, s, Me-19), 0.82 (3 H, s, Me-20).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (C-15), 68.0 (C-12), 62.7 (C-14), 59.9 (C-9), 57.4 (C-5), 50.8 (CO_2Me), 48.1 (C-13), 46.2 (C-8), 42.4 (C-3), 40.8 (C-1), 40.0 (C-7), 39.1 and 38.5 (SCH_2CH_2S), 36.9 (C-10), 36.3 (C-11), 33.4 (C-18), 33.0 (C-4), 27.0 (C-16), 21.2 (C-19), 18.9 (C-2), 18.2 (C-6), 17.1 (C-17), 15.6 (C-20).

EIMS: *m*/*z* (%) = 410 $(M)^+$ (8), 305 (22), 153 (44), 105 (78), 77 (100).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{38}O_2S_2$ $(M)^+$: 410.2313; found: 410.2317.

13*S*-11(12→13)-*abeo*-12-Ethylenedithiaisoanticopal-15-ol (4)

To a solution of **3** (211 mg, 0.5 mmol) in anhyd CH_2Cl_2 (9 mL) was added a solution of DIBALH in toluene (1.6 N, 0.7 mL, 1.02 mmol) under argon at –78 °C. The solution was stirred for 1 h, quenched by addition of MeOH (5 mL) and H_2O (5 mL), and extracted with Et_2O (3 × 100 mL). The organic layer was washed with H_2O (3 × 30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give **4**.

Yield: 180 mg (94%); colorless oily residue; $[\alpha]_D^{20}$ –12.6 (*c* 0.52, $CHCl_3$).

IR (neat): 3418, 2947, 1458, 1387, 1277, 1022 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.81 (1 H, s, H-12), 3.74 (1 H, dd, *J* = 11.2, 8.4, H-15_A), 3.60 (1 H, dt, *J* = 11.2, 5.6, H-15_B), 3.27–3.14 (4 H, m, SCH_2CH_2S), 1.83 (1 H, dt, *J* = 12.0, 2.8, H-7_A), 1.72 (1 H, dt, *J* = 12.0, 5.6, H-11_A), 1.63 (1 H, dt, *J* = 8.4, 5.6, H-14), 1.61–1.30 (9 H, m), 1.30–1.15 (2 H, m), 1.18 (3 H, s, Me-16), 1.00–0.80 (2 H, m), 0.83 (3 H, s, Me-18), 0.80 (3 H, s, Me-19), 0.79 (6 H, s, Me-20 and Me-17).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.1 (C-12), 60.5 (C-9), 60.3 (C-15), 59.3 (C-14), 57.5 (C-5), 47.3 (C-13), 45.1 (C-8), 42.4 (C-3), 41.5 (C-7), 40.1 (C-1), 38.8 and 38.5 (SCH_2CH_2S), 37.2 (C-11), 36.7 (C-10), 33.4 (C-18), 33.0 (C-4), 24.4 (C-16) 21.2 (C-19), 18.9 (C-2), 18.3 (C-6), 16.2 (C-17), 15.9 (C-20).

EIMS: *m*/*z* (%) = 382 $(M)^+$ (2), 245 (35), 191 (10), 105 (100), 69 (100).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{38}OS_2$ $(M)^+$: 382.2364; found: 382.2389.

13*S*-11(12→13)-*abeo*-12-Ethylenedithia-15-isoanticopalal (5) and 13*S*-11(12→13)-*abeo*-12-(2-Oxo)ethylenedithia-15-isoanticopalal (6)

Method A

To a stirred solution of **4** (716 mg, 1.88 mmol) in anhyd CH_2Cl_2 (19 mL) with 4 Å molecular sieves, were added NMO (460 mg, 3.4 mmol) and TPAP (64 mg, 0.18 mmol). The mixture was stirred for 1 h, then the solution was diluted with EtOAc (250 mL), filtered through a short pad of silica gel and Celite, and the solvent was evaporated to provide an oily residue. Column chromatography (silica gel; benzene) gave starting material (56.9 mg), compound **5** (324.1 mg, 45%) as a colorless solid, and an unseparated 1:1 mixture of **6a**,**b** as a colorless solid (198.9 mg, 27%). The ratio of the last compounds was calculated by integration of the signals in the ^1H NMR for hydrogens H-12 and H-15.

Method B

To a solution of pyridine (3.0 mL, 37.5 mmol) in anhyd CH_2Cl_2 (44 mL) was added CrO_3 (1.7 g, 17.4 mmol). The mixture was stirred for 15 min and then was added a solution of **4** (1.1 g, 2.9 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at r.t. for 15 min. Then the solution was diluted with EtOAc (100 mL) and filtered. The solid residue was washed with EtOAc (3 × 50 mL) and the combined organic layers were washed successively with aq NaOH (4%, 3 × 30 mL), aq HCl (2 N, 3 × 30 mL), aq $NaHCO_3$ (10%, 3 × 30 mL) and brine (3 × 30 mL), dried (Na_2SO_4) and evaporated to give a solid residue. The purification by silica gel chromatography (benzene) gave firstly **5** (672 mg, 61%), starting material (153 mg), and an unseparated 1:1 mixture of a colorless solid **6a**,**b** (132 mg, 11%). The ratio obtained for **6a**,**b** in this reaction was identical to the one obtained by method A.

5

Mp 137 °C (crystals were obtained from hexane–benzene); $[\alpha]_D^{20}$ +17.03 (*c* 1.18, $CHCl_3$).

IR (neat): 2930, 1709, 1456, 1387, 1044 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.91 (1 H, d, *J* = 3.2, H-15), 4.77 (1 H, s, H-12), 3.30–3.10 (4 H, m, SCH_2CH_2S), 2.20 (1 H, d, *J* = 3.2, H-14), 1.90 (1 H, dt, *J* = 12.0, 2.8, H-7_A), 1.71 (1 H, dd, *J* = 12.0, 5.6, H-11_A), 1.67–1.10 (10 H, m), 1.54 (3 H, s, Me-16), 1.04 (3 H, s, Me-18), 0.98–0.80 (2 H, m), 0.85 (3 H, s, Me-17), 0.84 (3 H, s, Me-19), 0.81 (3 H, s, Me-20).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.8 (C-15), 68.1 (C-12), 67.9 (C-14), 59.7 (C-9), 57.3 (C-5), 47.7 (C-8), 47.2 (C-13), 42.4 (C-3), 40.7 (C-7), 40.0 (C-1), 39.1 and 38.6 (SCH_2CH_2S), 37.8 (C-11), 36.9 (C-10), 33.4 (C-18), 33.0 (C-4), 26.0 (C-16), 21.2 (C-19), 18.5 (C-2), 18.2 (C-6), 17.6 (C-17), 15.7 (C-20).

EIMS: *m*/*z* (%) = 380 $(M)^+$ (1), 352 (15), 275 (6), 134 (8), 105 (100).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{36}OS_2$ $(M)^+$: 380.2208; found: 380.2207.

6a

^1H NMR (400 MHz, $CDCl_3$): δ = 9.88 (1 H, d, *J* = 2.4, H-15), 4.24 (1 H, s, H-12), 3.66 [1 H, ddd, *J* = 17.3, 12.5, 5.3, S(O)–CH_A], 3.48–3.30 [2 H, m, S(O)–CH_B and S–CH_B], 2.93 (1 H, ddd, *J* = 17.3, 14.4, 6.0, S–CH_A), 2.19 (1 H, d, *J* = 2.4, H-14), 2.05 (1 H, dd, *J* = 13.0, 6.1, H-7_A), 1.90–1.59 (7 H, m), 1.56 (3 H, s, Me-16), 1.50–1.10 (4 H, m), 1.09 (3 H, s, Me-18), 0.98–0.80 (2 H, m), 0.89 (3 H, s, Me-17), 0.87 (3 H, s, Me-19), 0.83 (3 H, s, Me-20).

6b

^1H NMR (400 MHz, $CDCl_3$): δ = 9.86 (1 H, d, *J* = 2.4, H-15), 4.20 (1 H, s, H-12), 3.61 [1 H, ddd, *J* = 16.3, 12.0, 4.8, S(O)–CH_A], 3.48–3.30 [2 H, m, S(O)–CH_B and S–CH_B], 2.83 (1 H, ddd, *J* = 16.3, 12.5, 6.6, S–CH_A) 2.18 (1 H, d, *J* = 2.4, H-14), 2.05 (1 H, dd, *J* = 13.0, 6.1, H-7_A), 1.90–1.59 (7 H, m), 1.52 (3 H, s, Me-16), 1.50–1.10 (4 H, m), 1.09 (3 H, s, Me-18), 0.98–0.80 (2 H, m), 0.88 (3 H, s, Me-17), 0.86 (3 H, s, Me-19), 0.83 (3 H, s, Me-20).

6a,b

IR (neat): 2940, 1717, 1458, 1387, 1045 cm^{-1}.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.2/203.5 (C-15), 90.9 (C-12), 69.2/70.3 (C-14), 60.0 (C-9), 57.3 (C-5), 47.7 (C-8), 47.2 (C-13), 42.2 (C-3), 40.7/40.6 (C-7), 40.1/40.0 (C-1), 38.0/57.2 (SCH_2CH_2S), 31.3 (C-11), 36.9 (C-10), 33.4 (C-18), 33.0 (C-4), 26.4/25.1 (C-16), 21.2 (C-19), 18.5/18.4 (C-2), 18.1 (C-6), 17.7 (C-17), 15.8 (C-20).

EIMS: *m*/*z* (%) = 396 $(M)^+$ (15), 352 (7), 191 (13), 105 (55), 84 (100).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{36}O_2S_2$ $(M)^+$: 396.2157; found: 396.2161.

(*E*/*Z*)-15a-homo-13*S*-11(12→13)-*abeo*-12-Ethylenedithia-15,15a-ene-15-methoxyisoanticopalane (7a,b)

To a suspension of methoxymethyltriphenylphosphonium chloride (1.5 g, 4.4 mmol) in anhyd THF (2.5 mL) under argon, was added a solution of NaHMDS in THF (1 M; 4.4 mL, 4.4 mmol) at –78 °C. The solution was stirred for 15–20 minutes and **5** (731 mg, 1.9 mmol) was added diluted in THF (3 mL) via cannula. The solution was stirred for 1 h until no starting material remained. The solution was quenched by addition of sat. aq NH_4Cl (5 mL) and extracted with Et_2O (3 × 100 mL). The organic layer was washed with H_2O (3 × 30 mL), dried (Na_2SO_4) and evaporated to provide a solid residue. Column chromatography (hexane–benzene, 8:2 and 1:1) gave an unseparated mixture of **7a**,**b** (*E*/*Z*, 1:4). The 1:4 ratio was established by integration of the signals for H-15 and H-15a.

Yield: 724 mg (92%); colorless oil.

7a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.18 (1 H, d, *J* = 12.4, H-15), 4.71 (1 H, s, H-12), 4.67 (1 H, dd, *J* = 12.4, 10.4, H-15a), 3.55 (3 H, s, MeO), 3.35–3.05 (4 H, m, SCH_2CH_2S), 2.58 (1 H, d, *J* = 10.4, H-14), 1.85–1.20 (12 H, m), 1.17 (3 H, s, Me-16), 0.98–0.80 (2 H, m), 0.83 (3 H, s, Me-18), 0.81 (3 H, s, Me-17), 0.80 (3 H, s, Me-19), 0.79 (3 H, s, Me-20).

7b

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.01 (1 H, d, *J* = 6.4, H-15), 4.78 (1 H, s, H-12), 4.36 (1 H, dd, *J* = 10.4, 6.4, H-15a), 3.55 (3 H, s, MeO), 3.35–3.05 (4 H, m, SCH_2CH_2S), 2.58 (1 H, d, *J* = 10.4, H-14), 1.85–1.20 (12 H, m), 1.17 (3 H, s, Me-16), 0.98–0.80 (2 H, m), 0.83 (3 H, s, Me-18), 0.81 (3 H, s, Me-17), 0.80 (3 H, s, Me-19), 0.79 (3 H, s, Me-20).

7a,b

IR (neat): 2920, 1659, 1462, 1381, 1271, 1109 cm^{-1}.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3 (C-15), 104.0 (C-15a), 68.7 (C-12), 59.4 (C-9, MeO), 57.6 (C-5), 55.5 (C-14), 47.0 (C-13), 46.9 (C-8), 42.5/42.4 (C-3), 40.2 (C-1), 39.2 (C-7), 39.0/38.2 (SCH_2CH_2S), 36.8 (C-10), 36.2 (C-11), 33.5 (C-18), 33.1 (C-4), 23.4 (C-16), 21.2 (C-19), 18.8 (C-2), 18.3 (C-6), 16.5 (C-17), 15.7 (C-20).

EIMS: *m*/*z* (%) = 408 $(M)^+$ (8), 308 (14), 271 (9), 245 (9), 205 (10), 155 (18), 105 (23).

HRMS (EI): *m*/*z* calcd for $C_{24}H_{40}OS_2$ $(M)^+$: 408.2520; found: 408.2523.

15a-homo-13*S*-11(12→13)-*abeo*-12-Ethylenedithia-15-isoanticopalal (8)

To a stirred solution of **7a**,**b** (394 mg 0.97 mmol) in acetone and H_2O (20 mL, 99:1) was added *p*-TsOH (48 mg, 0.23 mmol). After 8 h, the solution was poured into H_2O (5 mL) and extracted with Et_2O (3 ×100 mL). The organic layer was washed with aq $NaHCO_3$ (10%, 3 × 30 mL) and H_2O (3 × 30 mL), dried (Na_2SO_4) and concentrated by rotatory evaporation to give **8**.

Yield: 376 mg (98%); colorless oil; $[\alpha]_D^{20}$ –23.8 (*c* 0.64, $CHCl_3$).

IR (neat): 2930, 1724, 1464, 1385, 1275, 910, 733 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (1 H, dd, *J* = 4.0, 1.5, H-15), 4.76 (1 H, s, H-12), 3.36–3.08 (4 H, m, SCH_2CH_2S), 2.64 (1 H, ddd, *J* = 15.7, 5.0, 1.5, H_A-15a), 2.38 (1 H, ddd, *J* = 15.7, 9.3, 4.0, H_B-15a), 2.04 (1 H, dd, *J* = 9.3, 5.0, H-14), 1.73 (1 H, dd, *J* = 12.0, 5.6, H-11$_A$), 1.70–1.13 (11 H, m), 1.11 (3 H, s, Me-16), 1.02–0.85 (2 H, m), 0.83 (3 H, s, Me-18), 0.82 (3 H, s, Me-19), 0.81 (3 H, s, Me-17), 0.80 (3 H, s, Me-20).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.1(C-15), 68.1 (C-12), 59.3 (C-9), 57.4 (C-5), 53.6 (C-14), 46.4 (C-13), 45.4 (C-8), 42.4 (C-3), 42.3 (C-15a), 40.9 (C-7), 40.1 (C-1), 39.0 and 38.4 (SCH_2CH_2S), 36.7 (C-10), 36.3 (C-11), 33.4 (C-18), 33.0 (C-4), 24.1 (C-16), 21.2 (C-19), 18.8 (C-2), 18.3 (C-6), 16.3 (C-17), 15.8 (C-20).

EIMS: *m*/*z* (%) = 394 $(M)^+$ (1), 289 (12), 245 (100), 191 (7), 149 (18), 105 (80).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{38}OS_2$ $(M)^+$: 394.2364; found: 394.2368.

13*S*,16*R*-12-Ethylenedithia-19,25-epoxy-17(25),18-dienehyrtiosan-16-ol (9) and 13*S*,16*S*-12-Ethylenedithia-19,25-epoxi-17(25),18-dienehyrtiosan-16-ol (10)

To a solution of 3-bromofuran (0.1 mL, 1.1 mmol) in anhyd THF (2.5 mL) was added a solution of BuLi in hexane (1.6 M, 0.68 mL, 1.1 mmol) at –78 °C under argon. The solution was stirred for 10 min and **8** (288 mg, 0.7 mmol) was added diluted in THF (3 mL) via cannula. After 1 h the reaction was quenched by addition of a sat. aq NH_4Cl (2 mL) and extracted with Et_2O (3 × 100 mL). The ethereal extracts were washed with H_2O (3 × 30 mL) and brine (3 × 30 mL), dried (Na_2SO_4) and evaporated to provide an oily residue. Flash chromatography (benzene) gave **9** and **10**.

9

Yield: 148 mg, (44%); pale yellow oil; $[\alpha]_D^{20}$ +10.2 (*c* 1.26, $CHCl_3$).

IR (neat): 3440, 2920, 1462, 1385, 1159, 1022, 874 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (1 H, s, H-19), 7.39 (1 H, s, H-25), 6.42 (1 H, s, H-18), 4.81 (1 H, s, H-12), 4.73 (1 H, dd, *J* = 9.0, 4.2, H-16), 3.27–3.14 (4 H, m, SCH_2CH_2S), 1.92 (1 H, ddd, *J* = 13.2, 9.0, 4.2, H-15$_A$), 1.82–1.21 (15 H, m), 1.16 (3 H, s, Me-24), 1.00–0.88 (2 H, m), 0.89 (3 H, s, Me-20), 0.85 (6 H, s, Me-21 and Me-23), 0.82 (3 H, s, Me-22).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2 (C-19), 139.0 (C-25), 129.7 (C-17), 108.4 (C-18), 68.4 (C-12), 65.6 (C-16), 59.7 (C-9), 57.3 (C-5), 55.2 (C-14), 46.4 (C-13), 45.6 (C-8), 42.4 (C-3), 41.6 (C-7), 40.1 (C-1), 38.1 and 38.9 (SCH_2CH_2S), 36.7 (C-10), 35.4 (C-15), 35.1 (C-11), 33.4 (C-20), 33.0 (C-4), 24.8 (C-24), 21.2 (C-21), 19.0 (C-2), 18.3 (C-6), 16.1 (C-23), 15.8 (C-22).

FABMS: *m*/*z* (%) = 463 $(M + H)^+$ (3), 445 (3), 307 (19), 245 (9), 154 (100), 107 (28), 77 (27).

HRMS (FAB): *m*/*z* calcd for $C_{27}H_{43}O_2S_2$ $(M + H)^+$: 463.2704; found: 463.2701.

10

Yield: 106 mg (32%); pale yellow oil; $[\alpha]_D^{20}$ –12.8 (*c* 0.42, $CHCl_3$).

IR (neat): 3435, 2940, 1385, 1022 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (1 H, s, H-19), 7.39 (1 H, s, H-25), 6.48 (1 H, s, H-18), 4.79 (1 H, t, *J* = 6.7, H-16), 4.73 (1 H, s, H-12), 3.18–3.07 (4 H, m, SCH_2CH_2S), 1.91 (1 H, ddd, *J* = 12.9, 7.0, 6.5, H-15$_A$), 1.86–1.65 (5 H, m), 1.60–1.25 (9 H, m), 1.16 (3 H, s, Me-24), 1.10–0.90 (3 H, m), 0.88 (3 H, s, Me-20), 0.83 (3 H, s, Me-21), 0.82 (3 H, s, Me-23), 0.81 (3 H, s, Me-22).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2 (C-19), 139.8 (C-25), 128.6 (C-17), 108.8 (C-18), 68.2 (C-12), 65.3 (C-16), 59.6 (C-9), 57.3 (C-5), 55.1 (C-14), 46.8 (C-13), 45.6 (C-8), 42.4 (C-3), 41.7 (C-7), 40.0 (C-1), 38.9 and 38.2 (SCH_2CH_2S), 36.7 (C-10), 35.4 (C-15), 35.1 (C-11), 33.4 (C-20), 33.0 (C-4), 25.0 (C-24), 21.2 (C-21), 19.0 (C-2), 18.3 (C-6), 16.2 (C-23), 15.8 (C-22).

FABMS: *m*/*z* (%) = 463 $(M + H)^+$ (2), 445 (10), 307 (18), 245 (9), 191 (26), 154 (100), 105 (26), 69 (31).

HRMS (FAB): *m*/*z* calcd for $C_{27}H_{43}O_2S_2$ $(M+H)^+$: 463.2704; found: 463.2699.

13*S*,16*R*-19,25-Epoxy-17(25),18-diene-16-hydroxyhyrtiosan-12-al (11) and 13*S*,16*S*-19,25-Epoxy-17(25),18-diene-16-hydroxyhyrtiosan-12-al (12)

Method A

To a stirred solution of the dithiolanyl alcohol **9** (42 mg, 0.09 mmol) in THF and H_2O (2 mL, 99:1) was added $CaCO_3$ (11 mg) and aq $Hg(ClO_4)_2$ (2 M; 0.07 mL, 0.14 mmol) dropwise. The mixture was stirred for 10 min and then was diluted with Et_2O (20 mL) and filtered through a short pad of silica gel and a Celite column to give a mixture of both hydrohyaldehydes **12** and **11**. Column chromatography (benzene) afforded the hyrtiosal **12** (7 mg, 22%) and *epi*-hyrtiosal **11** (22 mg, 67%) both as colorless solids.

Experimental for **10** (100 mg, 0.22 mmol); yields **11** (23 mg, 29%) and **12** (48 mg, 57%).

11

$[\alpha]_D^{20}$ –27.1 (*c* 1.15, $CHCl_3$).

IR (neat): 2930, 1717, 1458, 1387, 1022 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (1 H, s, H-12), 7.38 (1 H, s, H-25), 7.33 (1 H, s, H-19), 6.39 (1 H, s, H-18), 4.49 (1 H, dd, *J* = 8.6, 6.1, H-16), 1.83–1.28 (13 H, m), 1.21 (3 H, s, Me-24), 1.19–0.87 (4 H, m), 0.86 (3 H, s, Me-20), 0.85 (3 H, s, Me-21), 0.83 (3 H, s, Me-23), 0.82 (3 H, s, Me-22).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.9 (C-12), 143.5 (C-19), 140.0 (C-25), 128.2 (C-17), 108.0 (C-18), 65.4 (C-16), 60.3 (C-9), 57.4 (C-5), 52.2 (C-13), 50.4 (C-14), 44.6 (C-8), 42.4 (C-3), 40.1 (C-1 and C-7), 36.8 (C-10), 33.8 (C-11), 33.4 (C-20, C-15), 33.0 (C-4), 21.2 (C-21), 18.9 (C-24), 18.8 (C-2), 18.2 (C-6), 16.4 (C-23), 15.6 (C-22).

FABMS: *m*/*z* (%) = 387 $(M + H)^+$ (2), 369 (23), 307 (13), 245 (7), 154 (100), 107 (37), 69 (37).

HRMS (FAB): *m*/*z* calcd for $C_{25}H_{39}O_3$ $(M+H)^+$: 387.2899; found: 387.2893.

12

$[\alpha]_D^{20}$ –62.2 (*c* 0.74, $CHCl_3$).

IR (neat): 2930, 1717, 1458, 1387 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.46 (1 H, s, H-12), 7.36 (2 H, s, H-25, H-19), 6.37 (1 H, s, H-18), 4.42 (1 H, t, *J* = 7.2, 6.0, H-16), 1.98 (1 H, dd, *J* = 8.0, 6.4, H-14), 1.90 (1 H, dd, *J* = 12.8, 6.0, H-11_A), 1.73 (1 H, dt, *J* = 12.4, 3.2, H-7_A), 1.70–1.02 (12 H, m), 1.19 (3 H, s, Me-24), 1.02–0.85 (2 H, m), 0.87 (3 H, s, Me-20), 0.86 (3 H, s, Me-21), 0.85 (3 H, s, Me-23), 0.83 (3 H, s, Me-22).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.6 (C-12), 143.2 (C-19), 138.7 (C-25), 129.2 (C-17), 108.4 (C-18), 64.2 (C-16), 60.3 (C-9), 57.4 (C-5), 52.8 (C-13), 48.1 (C-14), 44.5 (C-8), 42.4 (C-3), 40.2 (C-1 and C-7), 36.58 (C-10), 33.7 (C-15), 33.6 (C-11), 33.4 (C-20), 33.0 (C-4), 21.2 (C-21), 19.1 (C-24), 18.8 (C-2), 18.2 (C-6), 16.5 (C-23), 15.6 (C-22).

FABMS: *m*/*z* (%) = 387 $(M + H)^+$ (2), 369 (36), 307 (13), 245 (8), 191 (9), 154 (100), 91 (55), 69 (46).

HRMS (FAB): *m*/*z* calcd for $C_{25}H_{39}O_3$ $(M+H)^+$: 387.2899; found: 387.2902.

Method B

To a stirred solution of dithiolanyl alcohol **9** (91 mg, 0.20 mmol) in aq MeOH (2.5 mL, 99:1) was added $PhI(O_2CF_3)$ (27 mg, 0.1 mmol). The mixture was stirred for 10 min until no starting material remained, and then quenched by addition of aq $NaHCO_3$ (10%, 3 × 50 mL) and extracted into Et_2O (3 × 150 mL). The organic layer was washed with H_2O (3 × 50 mL), dried (Na_2SO_4) and evaporated to give a solid residue. Column chromatography (benzene) yielded *epi*-hyrtiosal **11** (11 mg, 15%) as a colorless solid.

Experimental for **10** (107 mg, 0.23 mmol); yield **12** (13 mg, 15%).

13*S*,16*S*-12-Ethylenedithia-19,25-epoxy-17(25),18-dien-16-acetoxyhyrtiosane (13)

To a solution of **10** (19.1 mg, 0.04 mmol) in pyridine (0.5 mL) was added Ac_2O (1 mL). The solution was stirred overnight and then was added onto ice. The solution was extracted with Et_2O (3 × 50 mL) and the organic extracts were washed successively with aq HCl (2 N; 3 × 25 ml), aq $NaHCO_3$ (3 × 25 mL) and H_2O (3 × 25 mL), dried (Na_2SO_4) and evaporated to yield **13**.

Yield: 20 mg (100%); $[\alpha]_D^{20}$ –14.6 (*c* 0.50, $CHCl_3$).

IR (neat): 1738, 1458, 1373, 1240, 1022, 874, 797, 733 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.49 (1 H, s, H-25), 7.39 (1 H, t, *J* = 18.0, H-19), 6.50 (1 H, s, H-18), 5.87 (1 H, dd, *J* = 9.0, 6.6, H-16), 4.68 (1 H, s, H-12), 3.30–3.05 (4 H, m, SCH_2CH_2S), 2.04 (3 H, s, $MeCO_2$), 1.98–1.02 (15 H, m), 1.14 (3 H, s, Me-24), 0.98–0.80 (2 H, m), 0.91 (3 H, s, Me-20), 0.83 (3 H, s, Me-21), 0.82 (3 H, s, Me-23), 0.81 (3 H, s, Me-22).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.7 ($MeCO_2$), 143.2 (C-19), 141.7 (C-25), 124.3 (C-17), 109.7 (C-18), 68.5 (C-12), 67.5 (C-16), 59.7 (C-9), 57.4 (C-5), 54.9 (C-14), 46.8 (C-13), 45.9 (C-8), 42.7 (C-7), 42.1 (C-3), 40.3 (C-1), 39.2 and 38.4 (SCH_2CH_2S), 37.0 (C-10), 35.9 (C-11 and C-15), 33.6 (C-20), 33.3 (C-4), 25.0 (C-24), 21.6 ($MeCO_2$), 21.5 (C-21), 19.3 (C-2), 18.6 (C-6), 16.3 (C-23), 16.0 (C-22).

EIMS: *m*/*z* (%) = 504 $(M)^+$ (2), 444 (20), 339 (14), 245 (100), 149 (24), 105 (44).

HRMS (EI): *m*/*z* calcd for $C_{29}H_{44}O_3S_2$ $(M)^+$: 504.2738; found: 504.2742.

13*S*,16*S*-19,25-Epoxy-17(25),18-dien-16-acetoxyhyrtiosan-12-al (14)

Compound **13** (20 mg, 0.04 mmol) was treated with $Hg(ClO_4)_2$ in similar conditions used for the formation of **11**/**12**, Method A, yielding after column chromatography ($CHCl_3$) **14**.

Yield: 14 mg (75%); colorless solid; $[\alpha]_D^{20}$ –58.8 (*c* 0.25, $CHCl_3$).

IR (KBr): 1719, 1458, 1389, 1250, 1157, 1026, 876, 822, 795, 725 cm^{-1}.

^{1}H (400 MHz, $CDCl_3$): δ = 9.35 (1 H, s, H-12), 7.40 (1 H, s, H-19), 7.37 (1 H, s, H-25), 6.35 (1 H, s, H-18), 5.69–5.62 (1 H, m, H-16), 2.03 (3 H, s, $MeCO_2$), 1.98–1.18 (15 H, m), 1.14 (3 H, s, Me-24), 1.05–0.82 (2 H, m), 0.90 (3 H, s, Me-20), 0.86 (3 H, s, Me-21), 0.85 (3 H, s, Me-23), 0.83 (3 H, s, Me-22).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.7 (C-12), 170.3 ($MeCO_2$), 143.2 (C-19), 140.8 (C-25), 124.5 (C-17), 108.7 (C-18), 66.7 (C-16), 60.1 (C-9), 57.2 (C-5), 52,3 (C-13), 48.8 (C-14), 44.6 (C-8), 42.3 (C-3), 40.7 (C-7), 40.1 (C-1), 36.8 (C-10), 33.5 (C-11), 33.4 (C-20), 33.0 (C-4), 30.6 (C-15), 21.2 ($MeCO_2$ and C-21), 19.1 (C-24), 18.8 (C-2), 18.2 (C-6), 16.3 (C-23), 15.6 (C-22).

EIMS: *m*/*z* (%) = 428 $(M)^+$ (9), 385 (6), 368 (32), 245 (100), 191 (25), 137 (44), 69 (76).

HRMS (EI): calcd for $C_{27}H_{40}O_4$ (M^+): 428.2927; found: 428.2967.

Compound 12; Saponification of 14

A solution of **14** (5 mg, 0.012 mmol) in MeOH (1 mL) was treated with methanolic K_2CO_3 (2.5%; 1 mL) and stirred for 2 h. Afterwards the reaction was quenched with H_2O (2 mL) and the MeOH was evaporated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the organic layer was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield **12**.

Yield: 5 mg (99%).

13*S*,16*R*-12-Ethylenedithia-19,25-epoxy-17(25),18-dien-16-acetoxyhyrtiosane (15)

Compound **9** (11 mg, 0.02 mmol) was acetylated in the same condition described for **13**, giving **15** in quantitative yield.

Yield: 12 mg (100%); colorless oil; $[\alpha]_D^{20}$ +25.5 (*c* 0.40, $CHCl_3$).

IR (neat): 1740, 1458, 1371, 1238, 1022, 874 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.46 (1 H, s, H-25), 7.38 (1 H, s, H-19), 6.42 (1 H, s, H-18), 5.80 (1 H, dd, *J* = 9.1, 5.7, H-16), 4.77 (1 H, s, H-12), 3.32–3.06 (4 H, m, SCH_2CH_2S), 2.06 (3 H, s, $MeCO_2$), 1.88–1.08 (15 H, m), 1.17 (3H, s, Me-24), 1.02–0.84 (2 H, m), 0.85 (3 H, s, Me-20), 0.83–0.81 (9 H, 3 s, Me-21, Me-22 and Me-23).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.4 ($MeCO_2$), 143.0 (C-19), 140.8 (C-25), 125.0 (C-17), 108.8 (C-18), 67.9 (C-12), 67.3 (C-16), 59.9 (C-9), 57.3 (C-5), 55.2 (C-14), 46.9 (C-13), 45.3 (C-8), 42.4 (C-7), 41.3 (C-3), 40.0 (C-1), 39.1 and 38.2 (SCH_2CH_2S), 36.7 (C-10), 34.7 (C-11 and C-15), 33.4 (C-20), 33.0 (C-4), 25.2 (C-24),

21.3 (*Me*CO_2), 21.2 (C-21), 18.9 (C-2), 18.3 (C-6), 16.2 (C-23), 15.7 (C-22).

EIMS: *m*/*z* (%) = 504 $(M)^+$ (1), 444 (6), 329 (19), 245 (100), 191 (12), 143 (18), 69 (39).

HRMS (EI): *m*/*z* calcd for $C_{29}H_{44}O_3S_2$ $(M)^+$: 504.2738; found: 504.2640.

13*S*,16*R*-19,15-Epoxy-17(25),18-dien-16-acetoxyhyrtiosan-12-al (16)

Compound **15** (12 mg, 0.02 mmol) was treated with $Hg(ClO_4)_2$ in similar conditions used for **11**/**12**, Method A, yielding after column chromatography ($CHCl_3$) **16**.

Yield: 7 mg (77%); colorless solid; $[\alpha]_D^{20}$ –3.0 (*c* 0.40, $CHCl_3$).

IR (KBr): 2938, 1738, 1715, 1391, 1366, 1238, 1018, 941, 874, 799 cm^{-1}.

^1H (400 MHz, $CDCl_3$): δ = 9.33 (1 H, s, H-12), 7.41 (1 H, s, H-25), 7.39 (1 H, s, H-19), 6.38 (1 H, s, H-18), 5.54 (1 H, dd, *J* = 9.2, 6.0, H-16), 2.00 (3 H, s, *Me*CO_2), 1.92–1.36 (14 H, m), 1.25 (3 H, s, Me-24), 1.18–0.90 (3 H, m), 0.88 (3 H, s, Me-20), 0.84 (3 H, s, Me-21), 0.83 (3 H, s, Me-23), 0.80 (3 H, s, Me-22).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.0 (C-12), 170.1 (Me*C*O_2), 143.2 (C-19), 141.6 (C-25), 123.8 (C-17), 108.5 (C-18), 67.4 (C-16), 60.1 (C-9), 57.3 (C-5), 52.3 (C-13), 49.5 (C-14), 44.7 (C-8), 42.3 (C-3), 40.1 (C-7, C-1), 36.7 (C-10), 33.7 (C-11), 33.4 (C-20), 33.0 (C-4), 30.6 (C-15), 21.3 (*Me*CO_2), 21.2 (C-21), 18.9 (C-24), 18.8 (C-2), 18.2 (C-6), 16.4 (C-23), 15.6 (C-22).

EIMS: *m*/*z* (%) = 428 $(M)^+$ (10), 386 (24), 368 (43), 325 (7), 245 (100), 191 (28), 123 (48), 69 (84).

HRMS (EI): *m*/*z* calcd for $C_{27}H_{40}O_4$ (M^+): 428.2927; found: 428.2937.

Compound 11; Saponification of 16

Compound **16** (12 mg, 0.05 mmol) was treated under the same conditions used for the saponification of **14**, yielding **11**.

Yield: 11 mg (99%).

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