Abstract: Isomeric cheilanthane sesterterpenoids have been obtained stereospecifically by two different synthetic pathways. Superacidic, low-temperature cyclization of C25 substrates (13E-bicyclogeranylfarnesoic acid methyl esters) led to 14α-cheilanthanes, along with other compounds, whereas the side-chain extension of a C20 precursor (ent-isocopalic alcohol) afforded 14β-cheilanthanes. The synthesized compounds could be considered as useful synthons in the preparation of bioactive natural cheilanthanes and structurally related sesterterpenoids.

Key words: terpenoids, cyclizations, rearrangements, synthesis, esters

Sesterterpenoids are widely distributed in nature, particularly in marine organisms. Two groups of marine sesterterpenoids, cheilanthanes and scalaranes, are of special interest due to their biological activity, especially as selective inhibitors of human phospholipase A2. Since natural sources provide only limited amounts of these compounds, a number of synthetic strategies have been devised in order to make them more accessible for further studies. Scalaranes have been extensively explored from the synthetic point of view, with most of the reported syntheses based on a biomimetic cyclization sequence of suitably constructed aliphatic or bicyclic C25 substrates. On the other hand, reports on the chemical synthesis of cheilanthanes are not so numerous in the literature. The basic problem in the synthesis of these compounds is the lateral chain attachment to the readily available isocopalic compounds, which is hampered by steric hindrance around the carbon at position 14 of the isocopalic skeleton. Cheilanthanes are, however, important compounds both in their own right and as precious intermediates in the synthesis of rare functionalized scalaranes. We report, in the present paper, our results on the synthesis of cheilanthanes with two possible orientations of the lateral prenyl chain. The cheilanthanic skeleton was constructed employing two different strategies. The first strategy was based on a superacidic cyclization of a C25 substrate to provide cheilanthanes with the 14α-orientation of the prenyl chain. The second method was based on the side-chain extension of a suitable optically active C20 tricyclic precursor, and allowed stereospecific preparation of 14β-cheilanthanes.

In the course of our investigation of cyclic terpenoids synthesis, we have recently reported the cyclization reaction of bicyclogeranylfarnesoic esters, obtained from manool 1, exhibiting the internal 13Z-double bond (Scheme 1). Along with scalarane compounds, cheilanthane and rearranged cheilanthane sesterterpenes were obtained as predominant reaction products. On the basis of molecular model simulations, it was assumed that the cyclization sequence was stopped by a specific conformational effect of the 13Z-double bond, which led to 14α-orientation of the lateral chain in the final cheilanthane products.

With the aim of preparing cheilanthanes with the more common 14β-configuration, we decided to investigate the superacid-induced cyclization of bicyclic sesterterpene substrates and, in particular, of 13E-isomers of bicyclogeranylfarnesoic esters 2 and 3. The superacidic cyclization of these esters has already been reported to lead, in a structurally selective manner, to scalaranes 4 and 5 under the action of fluorosulfonic acid (FSO₃H, 20 to 25 equivalents) under relatively harsh reaction conditions (–40 to –45 °C). In the present work we considered the possibility of selectively obtaining partially cyclized compounds, with the cheilanthane framework, using the same
starting compounds, 2 and 3, but employing milder conditions, namely lower concentrations of FSO\(_3\)H and lower temperatures (\(-78^\circ\)C).

Isomeric (13\(E\), 17\(E\))- and (13\(E\), 17\(Z\))-bicyclogeranylfarnesic esters 2 and 3 were prepared from manool 1 as previously reported. Using the reaction conditions described previously, both compounds were then submitted to superacidic cyclization with fluorosulfonic acid at \(-78^\circ\)C and quenched with a solution of Et\(_3\)N in \(n\)-hexane (1:1) (Scheme 2).

Cyclization of 2, followed by hydrolysis under the conditions described previously, gave, in addition to the expected product 4, a mixture of compounds which chromatographic TLC analysis showed to contain a number of non-acidic, unhydrolyzed compounds. In order to separate the unsaponified fraction from the acidic fraction, the crude, partially hydrolyzed mixture was subjected to flash chromatography on a silica gel column to separate the unsaponified fraction from the acidic fractions. The pooled acidic fractions was treated with diazomethane and analyzed by HPLC in order to determine the relative ratio of the obtained esters (Table 1).

In a preparative experiment, the mixture of tricyclic sesquiterpene esters was submitted to reverse-phase HPLC, affording cheilanthanes 6, 7, and 8, in order of retention time. The rearranged ester 7, previously obtained by an analogous cyclization reaction starting from the corresponding 13\(Z\)-bicyclogeranylfarnesic ester, was identified by spectral data (\(^1\)H, \(^1\)C NMR, IR, MS). The structures of the novel cheilanthanes 6 and 8 were determined by spectroscopic methods as described below.

The molecular formula, C\(_{26}\)H\(_{42}\)O\(_2\), of 6 was deduced from the mono-sodium molecular ion peak in the HRESIMS spectrum at \(m/z\) 409 [M + Na\(^+\)], which also indicated six degrees of unsaturation. The \(^1\)H NMR spectrum showed signals attributable to four tertiary methyls [singlets at \(\delta = 0.83, 0.88\) (6H), and 0.89], a 3H singlet at \(\delta = 3.69\) assigned to \(-CO_2Me\) group and two 3H broad singlets at \(\delta = 1.65\) and 2.18 due to two vinyl methyls. In addition, two \(^1\)H signals attributable to olefinic protons were observed at \(\delta = 5.24\) (H-12, sharp m) and 5.69 (H-18, br s). \(^1\)C NMR spectrum displayed signals due to sp\(^2\) carbons at \(\delta = 114.9\) (d), 119.9 (d), 136.0 (s), 160.7 (s), and 167.3 (-CO), indicating the presence of two trisubstituted double bonds, one of which was \(\alpha,\beta\)-unsaturated. Together, these data suggested a tricyclic skeleton for compound 6. Analysis of NMR homo- and hetero-correlation experiments led to a cheilanthane framework as depicted in 6. The \(\alpha\)-orientation of the prenyl chain at C-14 was suggested by both the down-field shifted \(^1\)C NMR value for C-23 (\(\delta = 23.3\)) and the up-field shifted values for C-7 (\(\delta = 37.4\)) and C-9 (\(\delta = 47.2\)).

Compound 8 was isomeric with 6 as indicated by both EIMS and \(^1\)C NMR data. Comparison of proton and carbon NMR spectra (see Experimental Section) clearly showed the presence of the same carbon skeleton exhibiting six methyl groups, four of which were tertiary (3H singlets at \(\delta = 0.82, 0.83, 0.85\), and 0.94), and the remaining two linked to sp\(^2\) carbons (3H broad singlets at \(\delta = 1.57\) and 2.19), together with an ester methoxy group (3H singlet at \(\delta = 3.69\)). The \(^1\)H NMR spectrum of 8 displayed a signal at \(\delta = 5.69\), due to the olefinic proton of a trisubstituted \(\alpha,\beta\)-unsaturated double bond, the same as 6, whereas the second vinyl signal was absent. Analysis of the \(^1\)C NMR spectrum of 8 indicated a different position of the double bond in the ring C. In particular, a tetrasubstituted double bond was located between C-13 and C-14 [\(\delta = 126.6\) (s, C-13); 139.4 (s, C-14)].

The superacidic, low-temperature cyclization of ester 3 was conducted in the same manner as described for 17\(E\)-isomer 2 above, affording, after the same work-up, 18-epi-scalaranic ester (5) and cheilanthanes 9 and 10, which were the 17\(Z\)-isomers of compounds 6 and 8, respectively. Compound 9 was identical to the compound previously obtained by the analogous cyclization of the corresponding 13\(E\)-bicyclogeranylfarnesic ester, whereas the structure of 10 was assigned by spectroscopic methods.

![Scheme 2](image-url)

The formation of 14α-cheilanthanes 6, 7 and 9 from substrates 2 and 3 with the 13E-stereochemistry was, however, quite surprising. According to the trans-antiparallel addition principle for the electrophilic cyclization of regular terpenoids, the opposite configuration at C-14 should be expected. When the reaction of substrate 2 was repeated under a range of reaction conditions (substrate:cyclization-agent ratio and/or reaction time), the same scalarane and cheilanthane products were obtained, but with different relative distributions (Table 1). In particular, the amount of scalarane 4 increased with respect to cheilanthanes (compounds 6–8) by enhancing either the concentration of cyclization agent (entries 1–4) or the reaction duration (entries 5, 6 and 8).

The cyclization reaction course could be rationalized as illustrated in Scheme 3. Formation of scalarane compound 4 can be explained by path ‘a’. Protonation of ester 2 to the carbocation I in the chair conformation (in equilibrium with the corresponding boat conformation II), should lead to the tricyclic ion III and then to the ion IV which, after deprotonation, should provide the tetracyclic scalarane 4. At the same time, formation of tricyclic 17E-cheilanthanic compounds 6 and 8 could take place via path ‘b’ from ion II, that should cyclize into tricyclic ion V. This carbocation could be deprotonated either at C-12 to give compound 6 or at C-14 to give compound 8. The rearranged cheilanthane 7 is proposed to originate from V through a s1,2-shift of the methyl group from C-8 to C-14. It seems that at lower concentrations of cyclizing agent and/or shorter reaction times, the boat conformation of the reaction intermediate II is favoured, since this leads to observed cheilanthanic compounds. Conversely, increasing the amount of fluorosulfonic acid and/or reaction time seems to favor the chair conformation of ion I, leading to the scalarane compound 4.

The preparation of cheilanthanes, exhibiting the more common β-configuration at C-14 (compounds 11 and 12), was conducted starting from a suitable optically active C20 tricyclic precursor. According to procedures already reported for the synthesis of racemic and optically active 13 cheilanthanes, the synthetic strategy used was based on the side-chain-extension method depicted in Scheme 4.
The starting material was ent-isocopalenol 13, which was easily derived from (–)-sclareol 14 by a known method. The alcohol 13 was transformed into the corresponding mesylate 15, that was coupled with sodium—ethyl acetate in toluene, to give ethylcarboxy-ent-isocopyalylacetone 16, along with ent-isocopoly-12,14-diene 17 and ent-isocopalenol 13. Compound 16 was decarboxylated with reflushing ethanolic NaOH to give ent-isocopyalylacetone 18. This compound was then submitted to Wittig—Horner reaction with trimethylphosphonoacetate to afford a mixture of the two isomeric 17Z- and 17E-cheilanthanic esters 11 and 12, which were purified by silica-gel and HPLC chromatography. The β-configuration of the prenyl chain at C-14 was clearly indicated by 13C NMR data. In fact, the carbon spectra of both 11 and 12 displayed up-field shifted values for C-3 (δ = 14.3 in both 11 and 12) and down-field shifted values for C-7 (δ = 40.6 in 11, 40.7 in 12) and for C-9 (δ = 55.0 in both 11 and 12) compared with those of the corresponding 14α-epimers, according to literature data for natural 14β-cheilanthanes.

In summary, optically active cheilanthane methyl esters have been prepared by two different methods. In particular, 14α-cheilanthanes have been synthesized by superacidic cyclization of a bicyclic sesterterpene precursor, easily obtained from manool, whereas the corresponding 14β-epimers have been synthesized by side-chain extension of a diterpene precursor, prepared from (–)-sclareol.

IR spectra were taken on a Bio-Rad FTS 7 spectrophotometer. 1H and 13C NMR spectra were recorded in CDCl3 on Bruker AM 400 and Bruker WM 300 spectrometers; chemical shifts are reported in ppm and are referred to CHCl3 as internal standard (δ = 7.26 for proton and δ = 77.0 for carbon). Optical rotations were measured in CHCl3 on a Jasco DIP 370 polarimeter, using a 10 cm cell. Low resolution EIMS were determined at 70 eV on a HP-GC 5890 series II mass spectrometer. High resolution ESIMS were performed on a Micromass Q-TOF MicroTM. The work-up of the reaction mixtures in organic solvents included exhaustive extraction with Et2O and washing with H2O up to neutral pH, drying over anhydrous Na2SO4, filtration and removal of the solvent in vacuo. Commercial Merck silica gel 60 (70–230 mesh ASTM) was used for flash chromatography, and Merck precoated silica gel plates were used for TLC. The chromatograms were sprayed with 0.1% cerium (IV) sulfate, filtration and removal of the solvent in vacuo. Commercial Merck silica gel 60 (70–230 mesh ASTM) was used for flash chromatography, and Merck precoated silica gel plates were used for TLC. The chromatograms were sprayed with 0.1% aq cerium (IV) sulfate in H2SO4 (2N) and heated at 80 °C for 5 min to detect the spots. Starting compound 13 was obtained from (–)-sclareol 14 following the literature procedure.

**Supercritical Cyclization of Methyl (13E,17E)-Bicyclogeranylfarnesolate (2)**

A solution of methyl (13E,17E)-bicyclogeranylfarnesolate 2 (300.0 mg, 0.77 mmol) in 2-nitropropane (8.0 mL) was cooled to −78 °C and treated under stirring, with a solution of FSO3H (0.47 M) in 2-nitropropane (8.2 mL), chilled to the same temperature and the mixture was stirred at −78 °C for 5 min. A soln of Et3N (~50% excess with respect to FSO3H) in light petroleum ether (Et3N–PE, 1:1) was then added and the reaction was allowed to warm to r.t. The reaction was extracted into Et2O (3 × 10 mL), washed with 10% aq H2SO4 (5 mL), H2O (2 × 5 mL), sat. NaHCO3 (5 mL) and H2O (2 × 5 mL), dried and filtered. The solvent was removed under vacuum to give a crude residue which was used in the next step without any purification. The residue (~298.0 mg) was dissolved in EtOH (5.0 mL) and NaOH (10% in EtOH, 20.0 mL) was added. The reaction mixture was refluxed for 2 h to give, after the same work-up, the crude reaction product (296.2 mg). Purification by column chromatography (Et2O–PE gradient) gave, in order of increasing polarity,
methyl scalaranate 4 (51.2 mg, 17%) and an acidic fraction (238.1 mg, 79%), which was methyalted with a saturated solution of CH₂N₂ in Et₂O (15.0 mL). After 20 min, the solvent was removed in vacuo and the crude reaction product was purified by silica gel chromatography (100% PE) to give a mixture of esters (240.2 mg). A sample of which (60.0 mg) was purified by HPLC (preparative Kromasil C₁₈ column, MeOH 100%, flow rate 2.4 mL/min), affording pure esters 6 (267.6 mg), 7 (134.3 mg), and 8 (10.3 mg).

The above procedure was used for each reaction listed in Table 1. The relative ratio of products 4, 6, 7 and 8 in the distinct entries was determined by analytical HPLC [Kromasil C₁₈ column, MeOH (100%), flow rate 1 mL/min].

**Methyl Scalaranate (4)**

Colorless crystals; Rᵢ = 0.62 (EtOAc–PE, 15%). All spectral data (δ₁H, IR, ¹H and ¹³C NMR) and melting point were identical to those of a standard sample.¹⁵

**Compound 6**

Colorless viscous liquid; Rᵢ = 0.61 (EtOAc–PE, 15%); [α]D²⁵ +59.7 (c 0.22, CHCl₃).

IR (film): 1720, 1652, 1018, 798 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 5.69 (1 H, br s, H-18), 5.24 (1 H, m, H-12), 3.69 (3 H, s, OMe), 2.19 (2 H, m, H-16), 2.18 (3 H, s, H-25), 1.90 (1 H, m, H-11b), 1.82 (1 H, m, H-11a), 1.68 (1 H, m, H-15b), 1.65 (3 H, s, H-24), 1.60 (3 H, m, H-2b and H-6b), 1.51 (1 H, m, H-7b), 1.40 (2 H, m, H-2a and H-6a), 1.35 (2 H, m, H-3b and H-15a), 1.18 (1 H, m, H-9), 1.32 (1 H, m, H-7a), 1.13 (1 H, m, H-3a), 1.16 (1 H, m, H-14), 0.88 (6 H, s, H₃-21 and H₃-22), 0.87 (3 H, s, H₃-23), 0.85 (1 H, m, H-1a), 0.83 (3 H, s, H-20), 0.82 (1 H, m, H-5).

¹³C NMR (75 MHz, CDCl₃): δ = 167.3 (s, C-19), 160.7 (s, C-17), 136.0 (s, C-13), 119.9 (d, C-12), 114.9 (d, C-18), 56.8 (d, C-5), 54.3 (d, C-14), 50.8 (q, OMe), 47.2 (d, C-9), 43.0 (t, C-16), 41.9 (t, C-3), 40.0 (t, C-1), 37.4 (s, C-10 or C-8), 37.4 (t, C-7), 37.2 (s, C-8 or C-10), 33.5 (q, C-21), 33.2 (s, C-4), 29.8 (t, C-6b), 28.9 (t, C-15), 23.5 (q, C-24), 23.3 (q, C-23), 23.1 (t, C-11), 21.9 (q, C-20), 19.1 (q, C-25), 18.6 (2 C, t, C-2 and C-6), 15.5 (q, C-22).

EIMS: m/z (%) = 386 (2) [M⁺], 371 (2), 355 (11), 327 (7), 312 (3), 281 (56), 259 (21), 253 (18), 207 (100), 191 (20), 177 (13), 163 (16), 149 (18), 135 (26), 119 (18), 109 (18), 95 (33), 81 (38), 67 (39), 55 (44).


**Superacid Cyclization of Methyl (13E,17Z)-Bicyclogeranyl-farnesate (3)**

Using the procedure described above, methyl (13E,17Z)-bicyclogeranyl-farnesate 2 (60.0 mg, 0.16 mmol) in 2-nitropropane (1.6 mL) was cooled to −78 °C and treated with FSO₃H (78.0 mg, 0.78 mmol) in 2-nitropropane (1.6 mL) under stirring. After 5 min, the reaction was stopped by adding a solution of Et₃N (0.4 mL) in PE (0.4 mL). The usual work-up gave a crude residue (59.0 mg) which was used in the next step without purification. The residue (59.0 mg) was dissolved in EtOH (0.4 mL) and a solution of NaOH (10% in EtOH, 1.0 mL) was added and the reaction mixture was refluxed for 2 h. The usual work-up gave a crude reaction product (58.0 mg), which was purified by silica-gel chromatography (EtO–PE gradient) to give, in order of increasing polarity, 18-épimethylscalaranate 5 (51.2 mg, 17%) and an acidic fraction (238.1 mg) which was further submitted to HPLC purification [preparative Kromasil C₁₈ column, MeOH (100%), flow rate 2.4 mL/min], affording pure esters 9 (12.7 mg) and 10 (3.2 mg).

18-épimethylscalaranate (5)

Colorless viscous liquid; Rᵢ = 0.64 (EtOAc–PE, 15%). All spectral data (δ₁H, IR, ¹H and ¹³C NMR) were identical to those of a standard sample.¹⁵

**Compound 9**

Colorless viscous liquid; Rᵢ = 0.65 (EtOAc–PE, 15%). All spectral data (δ₁H, IR, ¹H and ¹³C NMR) were identical to those of a standard sample.¹⁴

**Compound 10**

Colorless viscous liquid; Rᵢ = 0.65 (EtOAc–PE, 15%); [α]D²⁵ +37.3 (c 0.10, CHCl₃).

IR (film): 1718, 1650, 1169, 853 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ (selected peaks) = 5.62 (1 H, br s, H-18), 3.68 (3 H, s, OMe), 2.77 (1 H, d, J₉,₁₀ = 12, 12, 5 Hz, H-16a), 2.55 (1 H, d, J₉,₁₀ = 12, 12, 5 Hz, H-16b), 1.93 (3 H, d, J₉,₉ = 1 Hz, H-25), 1.66 (3 H, br s, H-24), 0.97 (3 H, s, H-23), 0.86 (3 H, s, H-21), 0.84 (3 H, s, H-22), 0.82 (3 H, s, H-20).

¹³C NMR (75 MHz, CDCl₃): δ = 166.6 (s, C-19), 160.2 (s, C-17), 139.8 (s, C-14), 126.7 (s, C-13), 115.4 (d, C-18), 56.6 (d, C-5), 56.5 (d, C-9), 50.8 (q, OMe), 42.2 (t, C-3), 39.7 (t, C-1), 39.5 (s, C-10), 38.5 (t, C-7), 37.5 (s, C-8), 34.3 (t, C-16 or C-23), 34.1 (t, C-12 or C-16), 33.3 (q, C-21), 33.2 (s, C-4), 26.1 (t, C-15), 25.1 (q, C-25), 24.1 (q, C-23 or C-20), 21.2 (q, C-20 or C-23), 19.4 (q, C-24), 18.9 (t, C-6 or C-2), 18.7 (t, C-2 or C-6), 17.9 (t, C-11), 17.9 (t, C-11), 16.5 (q, C-22).

Yield: 224.0 mg (93%); colorless viscous liquid; Rf = 0.52 (EtOAc–PE, 15%); [a]D25 = 37.1 (c 0.21, CHCl3).

**Compound 15**

A solution of alcohol 13 (190.0 mg, 0.65 mmol) in dry pyridine (12.0 mL) was cooled to 0 °C and treated with MesCl (0.6 mL, 0.9 g, 7.8 mmol) and DMAP (15.0 mg, 0.12 mmol). The reaction mixture was stirred at 0 °C for 6 h and then at rt for 12 h. The usual work-up gave a crude product (239.0 mg) which was purified by silica gel chromatography (Et2O–PE, 7%) to give the pure mesylate 15.

Yield: 224.0 mg (93%); colorless viscous liquid; Rf = 0.44 (Et2O–PE, 15%); [a]D25 = 37.1 (c 0.21, CHCl3).

**IR (film):** 2927, 2848, 1443, 1385, 1354, 1175, 974, 946, 821 cm⁻¹.

**1H NMR (300 MHz, CDCl3):** δ = 5.51 (1 H, br s, H-12), 4.42 (1 H, dd, JH–H = 3, 10 Hz, H-15a), 4.21 (1 H, dd, JH–H = 6, 10 Hz, H-15b), 3.00 (3 H, s, OSO2Me), 2.15 (1 H, br s, H-14), 2.06 (1 H, m, H-7a), 1.92 (2 H, m, H-11), 1.73 (3 H, br s, H-16), 1.63 (1 H, m, H-1a), 1.58 (2 H, m, H-2b and H-6b) and 1.39 (2 H, m, H-2a and H-6a), 1.26 (1 H, m, H-3b), 1.14 (1 H, m, H-9), 1.13 (1 H, m, H-3a), 0.89 (3 H, s, H-17), 0.86 (3 H, s, H-18), 0.82 (3 H, s, H-19), 0.81 (3 H, s, H-19), 0.79 (1 H, m, H-5), 0.81 (3 H, s, H-19), 0.79 (1 H, m, H-5), 0.81 (1 H, m, H-1b).

**13C NMR (75 MHz, CDCl3):** δ = 131.0 (s, C-13), 124.3 (d, C-12), 68.2 (t, C-15), 56.1 (d, C-5), 54.6 (d, C-9), 54.3 (d, C-14), 41.8 (t, C-3), 41.1 (t, C-7), 39.8 (t, C-11), 37.5 (q, OSO2Me), 37.3 (s, C-10 or C-8), 36.2 (s, C-8 or C-10), 33.4 (q, C-18), 33.1 (s, C-4), 22.5 (t, C-11), 21.6 (q, C-19 or C-16), 21.5 (q, C-16 or C-19), 18.6 (t, C-6 or C-2), 18.4 (t, C-2 or C-6), 15.7 (q, C-20 or C-17), 15.5 (q, C-17 or C-20).

**EIMS: m/z (%) = 272 (20) [M – MesSO2H]⁺, 257 (31), 237 (7), 229 (8), 216 (7), 207 (13), 191 (187), 176 (163), 213 (59), 200 (148), 519 (131), 809 (119), 100 (107), 65 (105), 91 (66), 81 (41), 69 (44), 55 (44).


**Coupling Reaction of ent-12-Isocoualen-15-yl Mesylate (15) with Ethyl Acetate**

Sodium metal (32.0 mg, 1.39 mmol) was added, under argon atmosphere, to a solution of ethyl acetate (196.0 mg, 1.50 mmol) in toluene (1.5 mL) and the mixture was refluxed for 15 min. A solution of mesylate 15 (120.0 mg, 0.33mmol) in toluene (1.2 mL) was then added and the reaction mixture was refluxed for 4 h. The usual work-up gave a crude product (125.0 mg) which was purified by silica gel chromatography with stepwise elution; 100% PE eluted compound 17 (31.9 mg, 36%), 1% Et2O–PE eluted a mixture of epimeric ketosteres 16 (36.7 mg, 28%) and 5% Et2O–PE eluted the starting compound 13 (32.2 mg, 34%).

**Mixture of Epimers 16**

Rf = 0.52 (EtOAc–PE, 15%).

**IR (film):** 1725 (s) cm⁻¹.

**1H NMR (300 MHz, CDCl3):** δ = 5.40 (1 H, br s, H-12), 4.20 (2 H, m, OCH2CH3), 2.25 (3 H, s, H-18 epimer a), 2.22 (3 H, s, H-18 epimer b), 1.67 (3 H, br s, H2-20), 1.30 (3 H, superimposed t, OCH2CH3, epimer a), 1.27 (3 H, superimposed t, OCH2CH3, epimer b), 0.87 (3 H, s, H-23), 0.85 (3 H, s, H-22), 0.81 (3 H, s, H-19), 0.75 (3 H, s, H-24).

**Compound 17**

White crystals; mp 93–94 °C (MeCN); Rf = 0.86 (EtOAc–PE, 15%); [a]D25 = +82.5 (c 0.16, CHCl3); Lit. [a]D25 = +66.4.

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Compound 11
Colorless viscous liquid; \( R_f = 0.65 \) (EtOAc–PE, 15%); \( [\alpha]_D^{25} = -17.9 \) (c 1.17, CHCl3).

IR (film): 2931, 1724, 1442, 1161 cm–1.

1H NMR (400 MHz, CDCl3): δ = 5.64 (1 H, br s, H-18), 5.37 (1 H, br s, H-12), 3.68 (3 H, s, OMe), 2.72 (2 H, m, H-1, H-17), 1.95 (1 H, m, H-7b), 1.92 (2 H, m, H2-15), 1.91 (3 H, s, H-25), 1.84 (2 H, m, H2-11), 1.77 (3 H, br s, H3-24), 1.68 (1 H, m, H-14), 1.60 (1 H, m, H-1b), 1.58 (2 H, m, H-2b and H-6b), 1.38 (1 H, m, H-3b), 1.37 (2 H, m, H-2a and H-6a), 1.16 (1 H, m, H-9), 1.15 (1 H, m, H-3a), 1.13 (1 H, m, H-7a), 0.87 (3 H, s, H-21), 0.86 (3 H, s, H-22), 0.83 (1 H, m, H-5), 0.82 (3 H, s, H-20), 0.79 (1 H, m, H-1a), 0.72 (3 H, s, H-3), 0.71 (1 H, br s, H-12), 3.69 (3 H, s, OMe), 2.36 (1 H, m, H-16a), 2.17 (3 H, s, OMe), 1.77 (3 H, s, OMe), 1.73 (1 H, m, H-1b), 1.67 (1 H, m, H-1a), 1.65 (1 H, m, H-14), 1.62 (1 H, m, H-1a), 1.58 (1 H, m, H-6a), 1.57 (3 H, s, H-24), 1.37 (3 H, m, H-2a, H-3b and H-6b), 1.35 (1 H, m, H-15a), 1.15 (1 H, m, H-9), 1.14 (1 H, m, H-3a), 1.06 (1 H, m, H-7b), 0.87 (3 H, s, H-22), 0.86 (3 H, s, H-20), 0.79 (1 H, m, H-1b), 0.73 (3 H, s, H-23).

13C NMR (75 MHz, CDCl3): δ = 166.8 (s, C-19), 160.6 (s, C-17), 135.0 (s, C-13), 122.2 (d, C-12), 115.6 (d, C-18), 56.2 (d, C-5), 55.6 (d, C-14), 55.0 (d, C-9), 50.8 (q, OMe), 41.9 (t, C-3), 40.6 (t, C-7), 39.8 (t, C-1), 37.9 (s, C-10 or C-8), 37.3 (s, C-8 or C-10), 35.8 (t, C-16), 33.5 (q, C-21), 33.3 (s, C-4), 25.6 (t, C-15), 25.3 (q, C-25), 22.8 (t, C-11), 22.0 (q, C-24 or C-20), 21.7 (q, C-20 or C-24), 18.8 (t, C-6 or C-2), 18.6 (t, C-2 or C-6), 15.5 (q, C-22), 14.3 (q, C-23).

EIMS: m/z (%) = 386 (23) [M]+, 371 (38), 355 (5), 346 (5), 273 (100), 269 (5), 221 (10), 205 (16), 189 (18), 163 (26), 143 (28), 137 (51), 123 (51), 109 (44), 95 (33), 81 (15), 69 (18).


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