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Synthesis and absolute configuration of (−)-chettaphanin I and (−)-chettaphanin II

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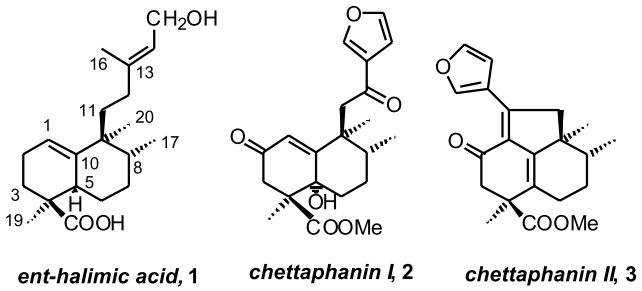
Abstract—An efficient synthesis of chettaphanin I and II has been achieved from *ent*-halimic acid. The absolute configuration of the natural products was established by nOe experiment and by X-ray analysis of chettaphanin II.

1. Introduction

The *ent*-halimans constitute a family of bicyclic diterpenes with a rearranged *ent*-labdane skeleton. Scarcely a hundred compounds from this family are known.[1] Chettaphanin I and II, isolated from *Adenochlaena siammensis* Ridl (Euphorbiaceae) in 1970[2] and 1971,[3] are the first known compounds of this class. Both compounds are the main components of 'chettaphangki' a digestive remedy used in folk medicine in Thailand. The structure of chettaphanin I and II were determined spectroscopically, chemically correlated and corroborated by X-ray crystallography of derivatives, the absolute configuration remaining unknown. Recently we have reported the synthesis and absolute configuration of chettaphanin II.[4]

Chettaphanin I and II are furanoditerpenoids that show functionalization at the same carbons, with the main characteristic of chettaphanin II being the double bond between C_1 and C_{12} of the *ent*-haliman skeleton that forms a third carbon ring.

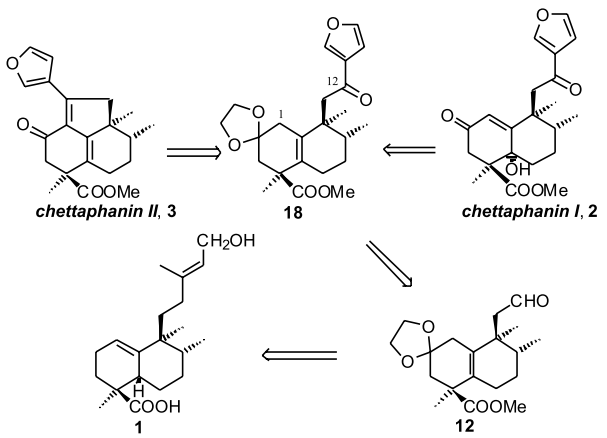
In this paper, we report the synthesis of chettaphanin I and II, starting from *ent*-halimic acid (the main component of *Halimium viscosum* (Villarino de los Aires) and a bicyclic diterpene of known absolute configuration[5] with an *ent*-halimane skeleton), confirming the structures and establishing the absolute configuration of the natural products. The *ent*-halimic acid has been used previously in the synthesis of *ent*-halimanolides[6] and sesterterpenolide[6] analogues of disidyolide[7] with interesting anti-tumour activity.



ent-halimic acid, 1 *chettaphanin I*, 2 *chettaphanin II*, 3

2. Results and discussion

In order to synthesize chettaphanin I **2** and chettaphanin II **3** from *ent*-halimic acid **1**, it is necessary to functionalize C_2 and C_{12} and to introduce a furyl group in the side chain; furthermore, for the synthesis of **2** it is necessary to introduce a hydroxyl group on C_5.



Scheme 1.

Keywords: chettaphanin I and II; *ent*-halimic acid; absolute configuration.

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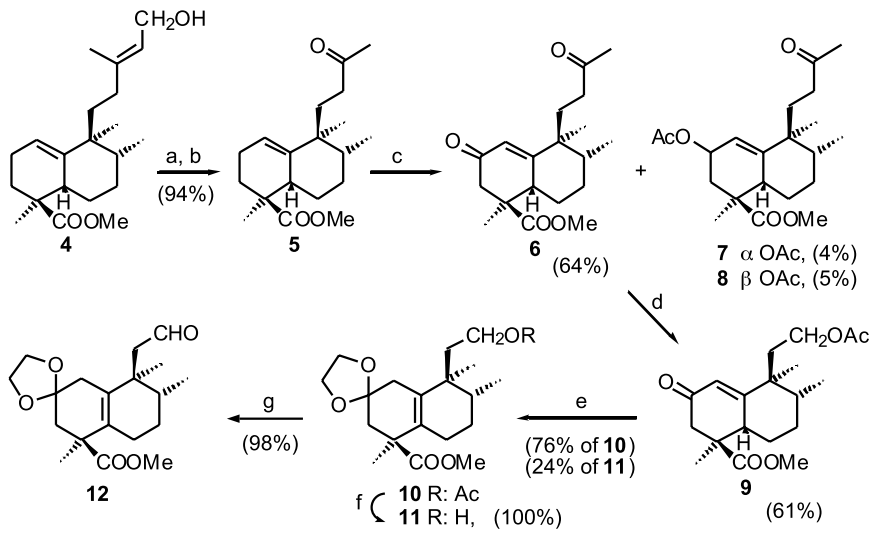


Scheme 2. (a) OsO_4, NMO, *t*-BuOH/THF/H_2O (7/2/1), 20 h; (b) LTA, C_6H_6, 20 min; (c) Na_2CrO_4, Ac_2O/AcOH, NaOAc, C_6H_6, 60°C, 15 h; (d) UHP/TFAA, CH_2Cl_2, 1 h; (e) ethylene glycol, *p*-TsOH, C_6H_6, reflux, 8 h; (f) 3% K_2CO_3 in MeOH, 2 h; (g) PDC, DMF, 3 h.

Scheme 1 shows the retrosynthesis for **2** and **3** from *ent*-halimic acid **1** through intermediate **18**. The furan ring of the side chain was added to a tetranor derivative **12** of *ent*-halimic acid **1**. The following steps describe the synthesis of intermediates **12** and **18** and transformation of the latter compound into **2** and **3**.

2.1. Degradation of the side chain and functionalization of A ring

The synthesis of **12** (Scheme 2), starting from **1**, requires the degradation of the side chain by four carbon atoms and oxidation of ring A at C_2. This has been achieved in a high yield in six steps.

The first two carbons were eliminated using the sequence of oxidation by OsO_4[8] followed by treatment with $Pb(OAc)_4$.[9] The oxidation of the methyl ester of *ent*-halimic acid **4** with OsO_4 was totally regioselective, only the side chain double bond reacting. The resulting triol was oxidized with LTA, giving ketone **5** in a 94% global yield for the two steps. The oxidation of **5** with Na_2CrO_4 in presence of Ac_2O/NaOAc[10] at 60°C gives the α,β-unsaturated ketone **6** (64%) and the minor products **7** (4%) and **8** (5%). The configuration at C_2 of **7** and **8** was established by nOe differential. The NMR ^1H signal of **8** centered at 5.31 ppm, corresponding to the geminal hydrogen at the secondary acetoxyl group in C_2, shows an nOe with methyls 19 and 20 that are on the α side of the molecule, so the acetoxyl group of **8** is β and the configuration of C_2 in **8** is *R*.

The remaining two carbons of the side chain were eliminated by a Bayer–Villiger reaction of **6** using trifluoroacetic acid anhydride in presence of urea-hydroperoxide[11] to give **9** in 61% yield.

In order to introduce the furan ring fragment in the side chain by means of an organometallic reagent, it was necessary to protect the carbonyl group at C_2 as a dioxolane. This was achieved by reaction of **9** with ethylene glycol in acidic media, giving a mixture of **10** and **11**. Subsequent saponification of **10** with K_2CO_3 in MeOH gave alcohol **11** in 100% global yield for two steps. Oxidation of **11** with PDC in DMF[12] gave aldehyde **12** in an excellent 98% yield.

2.2. Synthesis of the furan intermediate 18

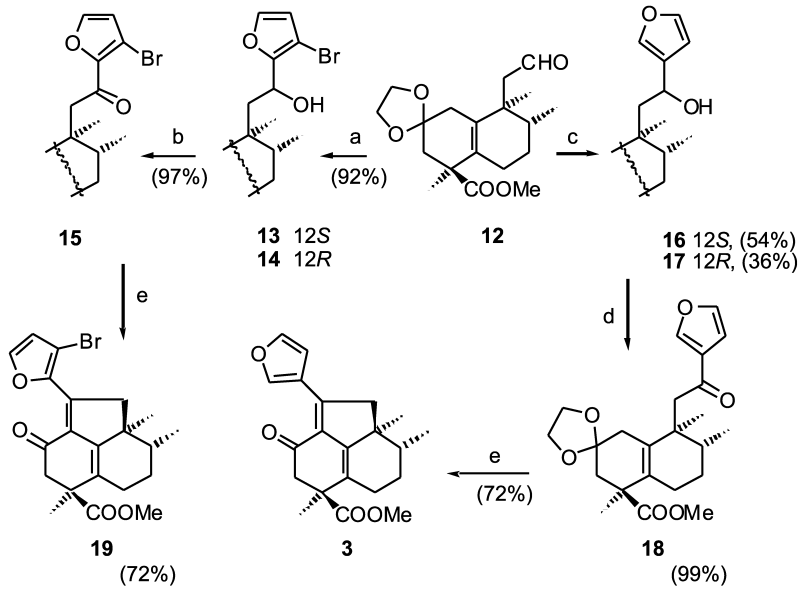
Treatment of **12** with 3-bromofurane/*n*BuLi at −78°C led to different results depending on the stoichiometry of the reaction for the synthesis of the furyl-lithium species.[13]

When the reaction is performed with a 3-bromofurane/*n*BuLi (2/1) ratio, at −78°C, a mixture of bromohydroxy-derivatives, epimers at C_{12} in **13/14**, was obtained, and could be separated by column chromatography (Scheme 3). TPAP/NMO[14] oxidation of **13** and **14** gives the same ketone **15** in quantitative yield.

The NMR ^1H spectra for **13** and **14**, are very similar and in both only signals corresponding to two aromatic hydrogens appear, so the aromatic fragment should have the bromine in it. The metalation position was fixed by nOe experiments; on irradiation of the signal at 7.32 ppm in the ^1H NMR spectrum of **13** a nOe was observed with the signal at 6.36 ppm; so both hydrogens are adjacent, and the metalation has taken place at C_2 in the 3-bromofurane. The C_{12} configuration of **13** and **14** was proposed by comparison with the NMR ^1H spectra of hyrtiosal[15] and its epimer at C_{16}. Epimers with *S* configuration in the carbon that has the secondary hydroxyl group show signals at higher field.

When the stoichiocometry of the metalation of 3-bromofurane with *n*BuLi is 1/1, at −78°C, and aldehyde **12** is added later on, the mixture of the hydroxyderivatives **16/17** is obtained quantitatively (Scheme 3).

The fundamental difference in the NMR ^1H spectra of **16** and **17** with those of **13** and **14** is the presence in this case of three aromatic hydrogens instead of two. This indicates that metalation has taken place in position 3 of the furan ring as expected. The configuration of **16** and **17** at C_{12} was



Scheme 3. (a) 3-Bromofurane, *n*BULi, (2/1), −78°C, 30 min; (b) TPAP/NMO; (c) 3-bromofurane, *n*BULi, (1/1), −78°C, 30 min; (d) TPAP/NMO; (e) *p*-TsOH, acetone, 5 h, rt.

proposed as in the above case, by comparison of the NMR ^{1}H spectra of **16** and **17** with hyrtiosal and its epimer. Oxidation of **16** and **17** with TPAP/NMO gives the same ketone **18**.

2.3. Synthesis of chettaphanin I and II

Treatment of **18** with *p*-TsOH led to **3** in a 72% yield (Scheme 3). Physical properties of **3** were coincident with those described in the literature for chettaphanin II,[3] whose structure has been confirmed by X-ray analysis.[4]

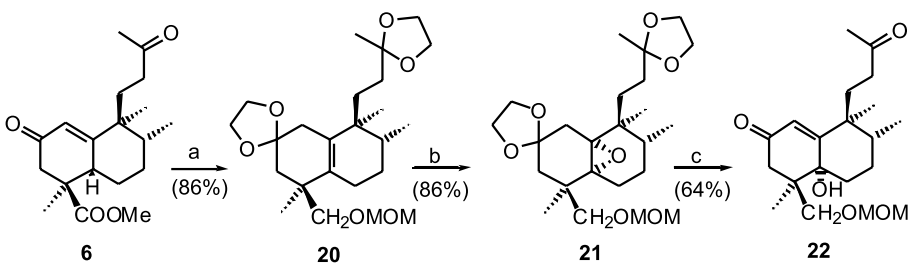
Treatment of **15** with *p*-TsOH led to **19** in a 72% yield, an analogue of **3** that was synthesized in order to test its biological activity.

The synthesis of the most interesting feature of chettaphanin I, an hydroxyl group γ to an α,β-unsaturated carbonyl in the bianular system, was tested in a model as **20**, previously obtained from **6**, in a parallel study in our laboratory,[16] by the successive reactions of protection of ketone groups, reduction of the ester and protection of the hydroxyl group with MOM (Scheme 4). Epoxidation with *m*-CPBA of **20** stereoselectively gives epoxide **21**, which on treatment under acidic conditions produced the deprotection of both carbonyl groups and opening of the epoxide to give ketone **22**, by protonation of the oxygen of the oxirane, carbocation formation at C_{10} and by loss of a proton at C_1 to give a double bond conjugated with the carbonyl on C_2. The opening of the epoxide takes place with retention of the configuration at C_5.

NMR ^{1}H/^{13}C studies, HMQC and HMBC of **22** make it possible to assign all the hydrogens in the molecule, the long-range signals corresponding to H_1, H_{19}, H_3 with C_5 being observed among others.

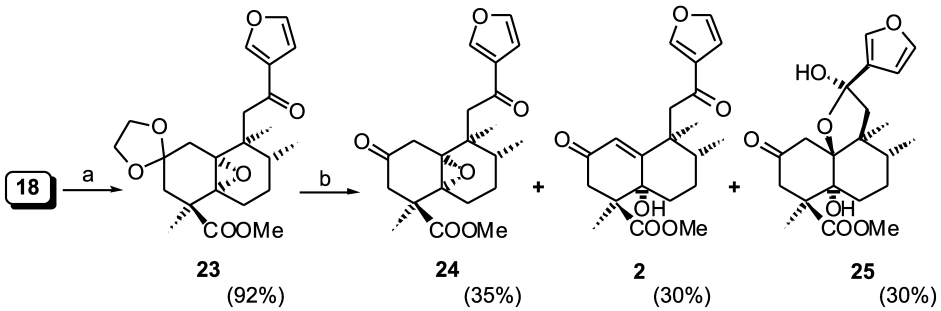
The configuration at C_5 of **22** was established by nOe experiments. In the NMR ^{1}H of **22** in DMSO the signal corresponding to the hydrogen of the hydroxyl group at C_5 was observed at 4.77 ppm. A nOe was observed between the hydrogens of C_{18} at 3.34 and 3.25 ppm with one of the hydrogens of C_3, $H_{3\beta}$. The irradiation of the signal at 4.77 ppm produces an increase in the signal of the other hydrogen at C_3, $H_{3\alpha}$, and a nOe was observed with Me_{20}, $H_{7\alpha}$ and $H_{6\alpha}$. Hence, the hydroxyl group is α and the configuration of C_5 is *S*. As the opening of the epoxide takes place with retention of the configuration at C_5, the epoxidation must have been stereoselective on the α side. The methodology used for the synthesis of **22** will be used for the synthesis of **2**.

Treatment of **18** with *m*-CPBA (Scheme 5) led to **23** with an excellent yield. Opening of the epoxide was tested under



6 20 21 22

Scheme 4. (a) 1. Ethylene glycol, *p*-TsOH, C_6H_6, reflux, 8 h; 2. LAH, Et_2O, 1.5 h; 3. DMM, BrLi, *p*-TsOH, 12 h, rt; (b) *m*-CPBA, Cl_2CH_2, 30 min, rt; (c) *p*-TsOH, acetone, 2 h, rt.



Scheme 5. (a) *m*-CPBA, Cl_2CH_2, 12 h, rt; (b) *p*-TsOH, acetone, 5 h, rt or $HClO_4$, 3 h, rt.

different conditions. Reaction of **23** with *p*-TsOH give a mixture of **2** (30%), **24** (35%) and **25** (30%) that was separated by column chromatography. When **23** was treated with $HClO_4$ (63%) at rt the same mixture was obtained in similar proportions.

Compound **24** come from deprotection of the carbonyl on C_2 of **23**.

Compound **25** shows in its NMR ^{13}C spectrum an hemiacetalic carbon (δ: 105.4 ppm) and in the ^1H NMR, H_{16} is shielded with respect to the equivalent proton of **23**, so C_{12} in **25** is not a carbonyl but a hemiacetal, due to its participation in the opening of the epoxide. (Fig. 1). The structure for **25** was corroborated by HMQC and HMBC experiments. For example H_{11} is correlated with carbons C_{12}(105.4), C_{13}(129.1), C_9(48.8), C_{10}(90.4) and C_8(34.9). The configuration at C_{12} corresponds to the more stable one based on stereoelectronic effects. It was not possible to do further studies due to instability.

Compound **2** shows in its ^{13}C NMR ($CDCl_3$) signals corresponding to two conjugated carbonyls at (197.6 and 190.8 ppm) and only one tetrasubstituted sp^3 carbon bonded to oxygen (δ: 72.7) corresponding to C_5, while at 125.6 (d) and 167.4 (s) ppm signals appear corresponding to the conjugated double bond to the carbonyl at C_2. Spectroscopic data suggest that the opening of the oxirane has taken place and has produced the desired group of conjugated carbonyl with an hydroxyl in the γ position. The $^1H/^{13}C$, HMQC and HMBC experiments corroborate this. The quaternary carbon at 72.7 ppm of C_5, is correlated with the olefinic hydrogen H_1, with the methylene of C_3 and with Me_{19} establishing the annular functionalization and so the structure of **2**. The absolute configuration of C_5 was established by nOe experiments

The ^1H NMR spectrum for **2** was done in DMSO and the signal for the hydrogen of the hydroxyl group observed at 5.01 ppm, this being analogous to the equivalent hydrogen of compound **22** in the nOe studies. By irradiation of the signal at 5.01 ppm, an increase of the signal at 2.60 ppm was observed, corresponding to the hydrogen $H_{3\alpha}$ and the Me_{20} signal at 1.20 ppm. This nOe establishes the position of the hydroxyl as α and so C_5 has the *S* configuration. Physical properties of **2** were coincident with those described in the literature for chettaphanin I,[2] so the natural product has the absolute configuration shown in the figures.

Opening of the epoxide of **23** takes place with retention of the configuration at C_5, so the epoxidation has been stereoselective for the α side and epoxide **23** has a 5*R*,10*R* configuration.

So (−)-chettaphanin I and (−)-chettaphanin II absolute configuration has been established.

3. Experimental

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. Melting points were determined with a Kofler hot stage melting point apparatus and are uncorrected. IR spectra were recorded on a BOMEM 100 FT IR spectrophotometer. ^1H and ^{13}C NMR spectra were performed in deuterochloroform and referenced to the residual peak of $CHCl_3$ at 7.26 and 77.0 ppm, for ^1H and ^{13}C, respectively, with a Bruker WP-200 SY or a BRUKER DRX 400 MHz spectrometer. Chemical shifts are reported in ppm and coupling constants (*J*) are given in Hz. MS were performed with a VG-TS 250 spectrometer with 70 eV ionizing voltage. Mass Spectra are presented as *m*/*z* (% rel. int.). HRMS were recorded at a VG Platform (Fisons) spectrometer using Chemical Ionization (ammonia as gas). Optical rotations were determined with a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether, THF and benzene were distilled from sodium, and pyridine and dichloromethane were distilled from calcium hydride under an Ar atmosphere.

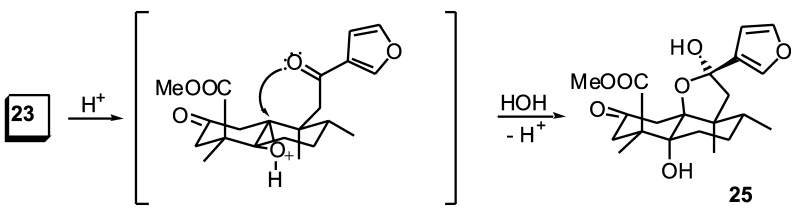


Figure 1.

3.1. Reaction of 4 with OsO_4/LTA: 5

To a solution of *ent*-halimic methyl ester **4** (6.82 g, 20.4 mmol) in *t*-BuOH/THF/H_2O (7/2/1, 200 ml) was added *N*-methylmorpholine *N*-oxide (NMO) (8.27 g, 61.2 mmol) and a solution of OsO_4 2.5% (1.1 ml, 0.01 mmol) in *t*-BuOH. The reaction mixture was stirred at room temperature for 20 h and a saturated aqueous solution of Na_2SO_3 (100 ml) was added. Extraction with AcOEt, followed by successive washing of the organic layer with a 10% aqueous $Na_2S_2O_3$ solution, 2N aqueous HCl solution, water and brine. The organic layer was dried and evaporated to yield the expected mixture of hydroxy derivatives (7.49 g, 99%): IR (film): 3439, 1728 cm^{-1}. To a solution of the hydroxy derivatives (7.19 g, 19.5 mmol) in benzene (100 ml) was added LTA (19.3 g, 43.6 mmol). The reaction mixture was stirred at room temperature for 20 min and then filtered off through celite. The solution was diluted with AcOEt and washed with a 6% aqueous solution of $NaHCO_3$, water and brine and then dried and evaporated to give a crude orange oil which was chromatographed on silica gel (hexane/AcOEt, 9/1) to give the expected ketone **5** (5.67 g, 94%).

3.1.1. Methyl 13-oxo-14,15-dinor-1(10)-*ent*-halimen-18-oate (5). $[\alpha]_D^{22}=+101.6°$ (c=1.25, $CHCl_3$); IR (film): 1726 cm^{-1}; ^1H NMR δ: 5.33–5.27 (1H, m, H_1), 3.61 (3H, s, –COOMe), 2.61 (1H, dd, J=12.6, 4.3 Hz, H_5), 2.4–1.9 (5H, m), 2.12 (3H, s, Me_{16}), 1.8–1.2 (8H, m), 1.07 (3H, s, Me_{19}), 0.83 (3H, s, Me_{20}), 0.76 (3H, d, J=7.0 Hz, Me_{17}); ^{13}C NMR δ: 120.2 (C_1), 23.1 (C_2), 29.8 (C_3), 44.9 (C_4), 38.2 (C_5), 23.3 (C_6), 28.6 (C_7), 39.0 (C_8), 42.7 (C_9), 141.3 (C_{10}), 32.6 (C_{11}), 38.9 (C_{12}), 209.5 (C_{13}), 29.8 (C_{16}), 15.6 (C_{17}), 178.1 (C_{18}), 21.0 (C_{19}), 22.1 (C_{20}), 51.5 (–COO*Me*); EIMS: 306 (M^+-18, 12), 229(42), 213(14), 175(100), 119(28), 105(41), 91(27); EIHRMS: calcd for $C_{19}H_{30}O_3$ (M^+) 306.2195, found (M^+) 306.2202.

3.2. Reaction of 5 with Na_2CrO_4: 6–8

Na_2CrO_4 (776 mg, 4.80 mmol), acetic anhydride (7.0 ml), acetic acid (3.8 ml) and NaOAc (572 mg) was added to a solution of ketone **5** (844 mg, 2.64 mmol) in benzene (6 ml) and stirred at 60°C for 15 h. The reaction mixture was then treated with ice, extracted with Et_2O and washed with a 10% aqueous solution of Na_2CO_3, water and brine. The organic layer was dried and evaporated to give a crude oil which was chromatographed on silica gel (hexane/AcOEt, 8/2→7/3→6/4) to give **5** (126 mg, 16%), the acetoxy derivates **7** (40 mg, 4%) and **8** (50 mg, 5%) and the expected compound **6** (540 mg, 64%).

3.2.1. Methyl 2,13-dioxo-14,15-dinor-1(10)-*ent*-halimen-18-oate (6). Mp: 83°C (*n*-hexane/Et_2O, 99/1); $[\alpha]_D^{22}=+186.0°$ (c=1.07, $CHCl_3$); UV (EtOH): 238 nm; IR (film): 1726, 1667, 1613, 1462, 1381, 1111 cm^{-1}; ^1H NMR δ: 5.79 (1H, s, H_1), 3.62 (3H, s, –COOMe), 2.99 (1H, dd, J=12.6, 4.3 Hz, H_5), 2.70 (1H, d, J_{AB}=16.1 Hz, H_{3A}), 2.5–2.0 (2H, m), 2.27 (1H, d, J_{AB}=16.1 Hz, H_{3B}), 2.12 (3H, s, Me_{16}), 1.9–1.7 (2H, m), 1.6–1.3 (5H, m), 1.21 (3H, s, Me_{19}), 0.94 (3H, s, Me_{20}), 0.79 (3H, d, J=6.9 Hz, Me_{17}); ^{13}C NMR δ: 125.1 (C_1), 196.5 (C_2), 42.9 (C_3), 46.3 (C_4), 40.8 (C_5), 23.5 (C_6), 28.2 (C_7), 40.7 (C_8), 44.8 (C_9), 169.1 (C_{10}), 32.2 (C_{11}), 38.3 (C_{12}), 208.1 (C_{13}), 29.8 (C_{16}), 15.6 (C_{17}), 176.6 (C_{18}), 21.9 (C_{19}), 20.6 (C_{20}), 52.2 (–COO*Me*); EIMS: 320 (M^+, 13), 219(9), 189(16), 43(18), 153(35), 121(57), 77(100); EIHRMS: calcd for $C_{19}H_{28}O_4$ (M^+) 320.1988, found (M^+) 320.1978; Anal. calcd for $C_{19}H_{28}O_4$: C, 71.21; H, 8.81, found: C, 71.07; H, 8.92.

3.2.2. Methyl 2α-acetoxy-13-oxo-14,15-dinor-1(10)-*ent*-halimen-18-oate (7). $[\alpha]_D^{22}=+18.0°$ (c=0.1, $CHCl_3$); IR (film): 1732, 1456, 1375, 1238, 1157, 1119, 1020 cm^{-1}; ^1H NMR δ: 5.37–5.31 (1H, m, H_2), 5.20 (1H, s, H_1), 3.63 (3H, s, –COOMe), 2.85 (1H, dd, J=12.6, 4.3 Hz, H_5), 2.5–1.9 (4H, m), 2.12 (3H, s, Me_{16}), 2.04 (3H, s, MeCOO–), 1.7–1.1 (7H, m), 1.12 (3H, s, Me_{19}), 0.84 (3H, s, Me_{20}), 0.80 (3H, d, J=7.0 Hz, Me_{17}); ^{13}C NMR δ: 120.7 (C_1), 69.1 (C_2), 33.3 (C_3), 44.6 (C_4), 38.1 (C_5), 23.9 (C_6), 28.6 (C_7), 39.8 (C_8), 43.2 (C_9), 146.6 (C_{10}), 32.0 (C_{11}), 38.6 (C_{12}), 209.5 (C_{13}), 29.7 (C_{16}), 15.5 (C_{17}), 177.1 (C_{18}), 21.6 (C_{19}), 21.3 (C_{20}), 51.9 (–COO*Me*), 21.3 (*Me*COO–), 170.7 (Me*C*OO–); EIMS: 364 (M^+, 5), 322(7), 262(23), 233(40), 173(100), 105(51); EIHRMS: calcd for $C_{21}H_{32}O_5$ (M^+) 364.2250, found (M^+) 364.2261.

3.2.3. Methyl 2β-acetoxy-13-oxo-14,15-dinor-1(10)-*ent*-halimen-18-oate (8). Mp: 96°C (*n*-Hexane); $[\alpha]_D^{22}=+85.4°$ (c=0.5, $CHCl_3$); IR (film): 1732, 1456, 1375, 1238, 1130, 1018 cm^{-1}; ^1H NMR δ: 5.34–5.28 (2H, m, H_1 and H_2), 3.64 (3H, s, –COOMe), 2.70 (1H, dd, J=12.6, 4.3 Hz, H_5), 2.5–1.8 (4H, m), 2.16 (3H, s, Me_{16}), 2.01 (3H, s, MeCOO–), 1.7–1.1 (7H, m), 1.16 (3H, s, Me_{19}), 0.90 (3H, s, Me_{20}), 0.78 (3H, d, J=7.0 Hz, Me_{17}); ^{13}C NMR δ: 119.4 (C_1), 68.1 (C_2), 36.4 (C_3), 44.1 (C_4), 38.3 (C_5), 22.9 (C_6), 27.9 (C_7), 38.5 (C_8), 42.8 (C_9), 146.6 (C_{10}), 32.6 (C_{11}), 38.7 (C_{12}), 209.3 (C_{13}), 29.9 (C_{16}), 15.5 (C_{17}), 177.0 (C_{18}), 19.6 (C_{19}), 21.3 (C_{20}), 51.8 (–COO*Me*), 21, 3 (*Me*COO–), 170.6 (Me*C*OO–); EIMS: 364 (M^+, 2), 233(42), 173(100), 105(51); EIHRMS: calcd for $C_{21}H_{32}O_5$ (M^+) 364.2250, found (M^+) 364.2259.

3.3. Reaction of 6 with UHP/TFAA: 9

To an ice cooled suspension of α,β-unsaturated ketone **6** (123 mg, 0.384 mmol) and UHP (890 mg, 9.45 mmol) in anhydrous DCM (6 ml), TFAA (0.29 ml, 2.05 mmol) was added under argon. The reaction mixture was stirred for 1 h, quenched via a very carefully dropwise addition of a 40% aqueous solution of $NaHSO_3$ and stirred for 1.5 h. Extraction with Et_2O, washing with a 6% aqueous solution of $NaHCO_3$ and water followed by drying and evaporation of the solvent left a crude yellow oil. Purification by flash chromatography on silica gel (hexane/AcOEt, 8/2→7/3→6/4) allowed the separation of the expected acetate **9** as a colourless oil (79 mg, 61%) and starting material **6** (32 mg, 26%).

3.3.1. Methyl 12-acetoxy-2-oxo-13,14,15,16-tetranor-1(10)-*ent*-halimen-18-oate (9). $[\alpha]_D^{22}=+110°$ (c=1.17, $CHCl_3$); UV (EtOH): 240 nm; IR (film): 1738, 1240, 1678 cm^{-1}; ^1H NMR δ: 5.84 (1H, s, H_1), 4.10–3.93 (1H, m, H_{12A}), 3.89–3.70 (1H, m, H_{12B}), 3.65 (3H, s, –COOMe), 3.10 (1H, dd, J=12.4, 4.8 Hz, H_5), 2.73 (1H, d, J_{AB}=16.1 Hz, H_{3A}), 2.27 (1H, d, J_{AB}=16.1 Hz, H_{3B}), 2.4–2.1 (2H, m), 2.03 (3H, s, MeCOO–), 1.9–1.7 (2H, m), 1.6–1.3

(3H, m), 1.23 (3H, s, Me_{19}), 1.05 (3H, s, Me_{20}), 0.80 (3H, d, J=7.5 Hz, Me_{17}); ^{13}C NMR δ: 125.0 (C_1), 196.7 (C_2), 43.3 (C_3), 46.4 (C_4), 40.8 (C_5), 23.4 (C_6), 28.2 (C_7), 40.4 (C_8), 44.1 (C_9), 168.1 (C_{10}), 37.3 (C_{11}), 61.2 (C_{12}), 15.2 (C_{17}), 176.6 (C_{18}), 21.6 (C_{19}), 20.9 (C_{20}), 52.5 (–COO*Me*), 170.8 (Me*C*OO–), 21.4 (*Me*COO–); EIMS: 336 (M^+, 17), 256(8), 217(59), 189(29), 161(28), 121(34), 91(40), 69(100); EIHRMS: calcd for $C_{19}H_{28}O_5$ (M^+) 336.1937, found (M^+) 336.1928.

3.4. Reaction of 9 with *p*-TsOH: 10 and 11

Acetate **9** (635 mg, 1.89 mmol) dissolved in benzene (35 ml), was refluxed in the presence of *p*-toluenesulfonic acid (10 mg, 0.06 mmol) and ethylene glycol (2.1 ml, excess) at 138°C for 8 h. The solution was diluted with Et_2O and washed with a 6% aqueous solution of $NaHCO_3$ and water. Evaporation of the solvent followed by chromatography on silica gel (hexane/AcOEt, 7/3→6/4) yielded the desired compound **10** (oil, 546 mg, 76%) and the **11** (oil, 150 mg, 24%).

3.4.1. Methyl 12-acetoxy-2-ethylenedioxy-13,14,15,16-tetranor-5(10)-*ent*-halimen-18-oate (10). $[\alpha]_D^{22}$=−19.1° (c=1.30, $CHCl_3$); IR (film): 1738, 1462, 1371, 1238, 1080, 1032 cm^{-1}; ^{1}H NMR δ: 4.2–3.8 (6H, m, $-OC_2H_4O-$ and H_{12}), 3.63 (3H, s, COOMe), 2.41 (1H, d, J=13.2 Hz, H_{3A}), 2.24 (2H, s, H_1), 2.01 (3H, s, MeCOO–), 1.8–1.5 (4H, m), 1.72 (1H, d, J=13.2 Hz, H_{3B}), 1.5–1.2 (3H, m), 1.33 (3H, s, Me_{19}), 0.88 (3H, s, Me_{20}), 0.87 (3H, d, J=6.7 Hz, Me_{17}); ^{13}C NMR δ: 35.8 (C_1), 107.5 (C_2), 42.0 (C_3), 48.9 (C_4), 130.9 (C_5), 24.9 (C_6), 26.5 (C_7), 34.1 (C_8), 39.8 (C_9), 132.7 (C_{10}), 35.6 (C_{11}), 61.6 (C_{12}), 15.9 (C_{17}), 177.2 (C_{18}), 23.7 (C_{19}), 20.9 (C_{20}), 51.9 (–COO*Me*), 170.9 (Me*C*OO–), 20.8 (*Me*COO–), 64.3 and 64.1 ($-OC_2H_4O-$); EIMS: 380 (M^+, 57), 321(11), 293(5), 261(73), 219(22), 153(33), 131(28), 107(48), 77(100); EIHRMS: calcd for $C_{21}H_{32}O_6$ (M^+) 380.2199, found (M^+) 380.2191.

3.4.2. Methyl 2-ethylenedioxy-12-hydroxy-13,14,15,16-tetranor-5(10)-*ent*-halimen-18-oate (11). $[\alpha]_D^{22}$=+0.1° (c=1.55, $CHCl_3$); IR (film): 3447, 1734, 1458, 1375, 1236, 1154, 1080, 1032 cm^{-1}; ^{1}H NMR δ: 4.0–3.8 (4H, m, $-OC_2H_4O-$), 3.70–3.52 (2H, m, H_{12}), 3.60 (3H, s, –COOMe), 2.30 (2H, s), 2.28 (1H, d, J=13.2 Hz, H_{3A}), 2.0–1.8 (2H, m), 1.8–1.6 (4H, m), 1.65 (1H, d, J=13.2 Hz, H_{3B}), 1.4–1.2 (1H, m), 1.30 (3H, s, Me_{19}), 0.85 (3H, s, Me_{20}), 0.85 (3H, d, J=6.6 Hz, Me_{17}); ^{13}C NMR δ: 36.0 (C_1), 107.4 (C_2), 42.5 (C_3), 48.7 (C_4), 130.9 (C_5), 25.0 (C_6), 26.7 (C_7), 35.0 (C_8), 40.0 (C_9), 133.3 (C_{10}), 41.0 (C_{11}), 59.6 (C_{12}), 16.2 (C_{17}), 177.5 (C_{18}), 24.2 (C_{19}), 21.5 (C_{20}), 51.9 (–COO*Me*), 64.3 and 64.1 ($-OC_2H_4O-$); EIMS: 338 (M^+, 29), 279(20), 219(18), 165(63), 131(22), 107(48), 77(100); EIHRMS: calcd for $C_{19}H_{30}O_5$ (M^+) 338.2093, found (M^+) 338.2086.

3.5. Hydrolysis of 10: 11

To **10** (100 mg, 0.263 mmol) a 3% solution of K_2CO_3 in methanol (3 ml) was added. After 2 h the solvent was evaporated and diluted with Et_2O. The organic layer was successive washed with a 2N aqueous solution of HCl and water and then dried and evaporated to yield the expected compound **11** (89 mg, 100%).

3.6. Oxidation of 11 with PDC: 12

To a solution of alcohol **11** (154 mg, 0.456 mmol) in DMF (8 ml), pyridinium dichromate (1.82 g, 4.54 mmol) was added. The reaction mixture was stirred for 3 h and then water (10 ml) was added. Extraction with Et_2O, followed by washing with water, dried and evaporation of the organic layer yielded **12** (oil, 68 mg, 98%).

3.6.1. Methyl 2-ethylenedioxy-12-oxo-13,14,15,16-tetranor-5(10)-*ent*-halimen-18-oate (12). $[\alpha]_D^{22}$=+2.1° (c=0.95, $CHCl_3$); IR (film): 1734, 1717, 1456, 1375, 1238, 1152, 1078, 1032 cm^{-1}; ^{1}H NMR δ: 9.63 (1H, s, H_{12}), 4.0–3.8 (4H, m, $-OC_2H_4O-$), 3.60 (3H, s, –COOMe), 2.6–2.2 (5H, m, H_{11}, H_1 and H_{3A}), 2.1–1.9 (1H, m), 1.62 (1H, d, J=13.2 Hz, H_{3B}), 1.8–1.6 (2H, m), 1.4–1.2 (2H, m), 1.31 (3H, s, Me_{19}), 0.96 (3H, s, Me_{20}), 0.88 (3H, d, J=6.7 Hz, Me_{17}); ^{13}C NMR δ: 36.4 (C_1), 107.2 (C_2), 42.2 (C_3), 48.8 (C_4), 131.3 (C_5), 24.5 (C_6), 26.2 (C_7), 36.4 (C_8), 40.1 (C_9), 131.7 (C_{10}), 51.2 (C_{11}), 204.3 (C_{12}), 15.7 (C_{17}), 177.0 (C_{18}), 23.9 (C_{19}), 21.1 (C_{20}), 51.9 (–COO*Me*), 64.3 and 64.1 ($-OC_2H_4O-$); EIMS: 336 (M^+, 6), 259(14), 233(38), 173(29), 153(22), 129(27), 105(45), 77(100); EIHRMS: calcd for $C_{19}H_{28}O_5$ (M^+) 336.1937, found (M^+) 336.1916.

3.7. Reaction of 12 with 3-bromofuran/*n*BuLi: 13 and 14

A solution of 3-bromofuran (0.076 ml, 0.500 mmol) in THF (1.5 ml) was treated dropwise with *n*BuLi (1.6 M in hexane, 0.16 ml, 0.250 mmol) at −78°C. After the reaction mixture was stirred for 30 min at this temperature a solution of aldehyde **12** (70 mg, 0.208 mmol) in dry THF (1.5 ml) was added. The mixture was stirred for 1 h at −78°C and then treated with a saturated NH_4Cl aqueous solution, extracted with Et_2O and washed with a 6% aqueous solution of $NaHCO_3$ and water. Evaporation of the solvent followed by chromatography on silica gel (hexane/AcOEt, 6/4) yielded **13** and **14** (92 mg, 92%).

3.7.1. Methyl 14-bromo-13,15-epoxy-2-ethylendioxy-12*S*-hydroxy-16-nor-15-homo-5(10),13,15-*ent*-halimatrien-18-oate (13). IR (film): 3470, 3123, 1732, 1464, 1377, 1242, 1078, 1032, 1011, 972, 883 cm^{-1}; ^{1}H NMR δ: 7.32 (1H, s, H_{15}), 6.36 (1H, s, H_{15a}), 5.04 (1H, dd, J=9.1, 3.2 Hz, H_{12}), 3.98–3.94 (4H, m, $-OC_2H_4O-$), 3.68 (3H, s, –COOMe), 2.41 (1H, d, J=13.2 Hz, H_{3A}), 2.3–2.0 (4H, m, H_1 and H_{11}), 1.8–1.6 (3H, m), 1.68 (1H, d, J=13.2 Hz, H_{3B}), 1.4–1.2 (2H, m), 1.37 (3H, s, Me_{19}), 0.94 (3H, s, Me_{20}), 0.92 (3H, d, J=6.7 Hz, Me_{17}).

3.7.2. Methyl 14-bromo-13,15-epoxy-2-ethylendioxy-12*R*-hydroxy-16-nor-15-homo-5(10),13,15-*ent*-halimatrien-18-oate (14). IR (film): 3470, 3123, 1732, 1464, 1377, 1242, 1078, 1032, 1011, 972, 883 cm^{-1}; ^{1}H NMR δ: 7.33 (1H, s, H_{15}), 6.36 (1H, s, H_{15a}), 5.06 (1H, dd, J=10.1, 3.4 Hz, H_{12}), 3.99–3.95 (4H, m, $-OC_2H_4O-$), 3.68 (3H, s, –COOMe), 2.61 (1H, d, J=13.2 Hz, H_{3A}), 2.4–2.0 (4H, m, H_1 and H_{11}), 1.82 (1H, d, J=13.2 Hz, H_{3B}), 1.8–1.7 (3H, m), 1.4–1.2 (2H, m), 1.37 (3H, s, Me_{19}), 0.92 (3H, s, Me_{20}), 0.84 (3H, d, J=6.7 Hz, Me_{17}).

3.8. Oxidation of 13 and 14 with TPAP/NMO: 15

To a mixture of **13/14** (30 mg, 0.062 mmol), *N*-methylmorpholine *N*-oxide (16 mg, 0.122 mmol) and molecular sieves (50 mg) in anhydrous DCM (2 ml), under argon, at room temperature was added TPAP (4 mg, 0.012 mmol). The reaction mixture was stirred for 30 min and then filtered on silica gel and celite (EtOAc), the organic layer was evaporated to yield the expected compound **15** (oil, 29 mg, 97%)

3.8.1. Methyl 14-bromo-13,15-epoxy-2-ethylendioxy-12-oxo-16-nor-15a-homo-5(10),13,15a-*ent*-halimatrien-18-oate (15). IR (film): 3123, 1732, 1674, 1549, 1476, 1377, 1244, 1155, 1076, 1034, 882, 735 cm^{-1}; ^1H NMR δ: 7.44 (1H, s, H_{15}), 6.60 (1H, s, H_{15a}), 3.95–3.91 (4H, m, $-OC_2H_4O-$), 3.67 (3H, s, –COOMe), 3.11 and 3.00 (1H, d, J_{AB}=15.1 Hz, H_{11}), 2.39 (1H, d, J=13.2 Hz, H_{3A}), 2.30 (2H, d, J=6.7 Hz), 2.13–2.10 (1H, m), 1.61 (1H, d, J=13.2 Hz, H_{3A}), 1.5–1.2 (4H, m), 1.33 (3H, s, Me_{19}), 1.03 (3H, s, Me_{20}), 0.87 (3H, d, J=6.9 Hz, Me_{17}); ^{13}C NMR δ: 36.2 (C_1), 107.4 (C_2), 42.1 (C_3), 48.5 (C_4), 129.6 (C_5), 23.2 (C_6), 25.7 (C_7), 33.3 (C_8), 41.4 (C_9), 131.9 (C_{10}), 45.5 (C_{11}), 188.9 (C_{12}), 148.7 (C_{13}), 106.2 (C_{14}), 117.5 (C_{15a}), 144.6 (C_{15}), 15.3 (C_{17}), 177.3 (C_{18}), 24.0 (C_{19}), 21.3 (C_{20}), 51.9 (–COO*Me*), 64.2 and 64.1 ($-OC_2H_4O-$); EIHRMS: calcd for $C_{23}H_{29}BrO_6$ (M^+) 481.3837, found (M^+) 481.3830.

3.9. Reaction of 12 with 3-bromofuran/*n*BuLi: 16 and 17

A solution of 3-bromofuran (0.038 ml, 0.250 mmol) in THF (1.5 ml) was treated dropwise with *n*BuLi (1.6 M in hexane, 0.16 ml, 0.250 mmol) at −78°C. After the reaction mixture was stirred for 30 min at this temperature a solution of aldehyde **12** (70 mg, 0.208 mmol) in dry THF (1.5 ml) was added. The mixture was stirred for 1 h at −78°C and then treated with a saturated NH_4Cl aqueous solution, extracted with Et_2O and washed with a 6% aqueous solution of $NaHCO_3$ and water. Evaporation of the solvent followed by chromatography on silica gel (hexane/AcOEt, 6/4) yielded **16** (oil, 38 mg, 54%) and **17** (oil, 25 mg, 36%).

3.9.1. Methyl 15,16-epoxy-2-ethylenedioxy-12*S*-hydroxy-5(10),13(16),14-*ent*-halimatrien-18-oate (16). $[\alpha]_D^{22}$= +4.6° (*c*=0.80, $CHCl_3$); IR (film): 3500, 1724, 1458, 1375, 1262, 1157, 1078, 1030, 665 cm^{-1}; ^1H NMR δ: 7.34 (2H, s, H_{15} and H_{16}), 6.39 (1H, s, H_{14}), 4.85 (1H, dd, J=9.0 and 2.2 Hz, H_{12}), 4.0–3.8 (4H, m, $-OC_2H_4O-$), 3.67 (3H, s, –COOMe), 2.38 (1H, d, J=12.5 Hz, H_{3A}), 2.35 (1H, d, J=10.5 Hz, H_{1A}), 2.15 (1H, d, J=10.5 Hz, H_{1B}), 2.00 (1H, dd, J=15.0, 9.4 Hz, H_{11A}), 1.72 (1H, d, J=15.0, 2.2 Hz, H_{11B}), 1.70 (1H, d, J=12.5 Hz, H_{3B}), 1.7–1.5 (2H, m), 1.4–1.2 (3H, m), 1.35 (3H, s, Me_{19}), 0.93 (3H, s, Me_{20}), 0.93 (3H, d, J=6.8 Hz, Me_{17}); ^{13}C NMR δ: 36.7 (C_1), 107.3 (C_2), 42.7 (C_3), 48.6 (C_4), 131.7 (C_5), 25.2 (C_6), 26.8 (C_7), 35.3 (C_8), 40.6 (C_9), 133.2 (C_{10}), 46.5 (C_{11}), 64.4 (C_{12}), 130.8 (C_{13}), 108.6 (C_{14}), 138.3 (C_{15}), 143.0 (C_{16}), 16.1 (C_{17}), 177.6 (C_{18}), 24.5 (C_{19}), 21.3 (C_{20}), 52.0 (–COO*Me*), 64.4 and 64.2 ($-OC_2H_4O-$); EIMS: 404 (M^+, 2), 292(37), 233(22), 189(10), 161(13), 91(46); EIHRMS: calcd for $C_{23}H_{32}O_6$ (M^+) 404.2199, found (M^+) 404.2191.

3.9.2. Methyl 15,16-epoxy-2-ethylenedioxy-12*R*-hydroxy-5(10),13(16),14-*ent*-halimatrien-18-oate (17). $[\alpha]_D^{22}$= −17.2° (*c*=0.50, $CHCl_3$); IR (film): 3500, 1730, 1464, 1377, 1159, 1089, 1030, 665 cm^{-1}; ^1H NMR δ: 7.38 (2H, s, H_{15} and H_{16}), 6.38 (1H, s, H_{14}), 4.91 (1H, dd, J=9.4, 2.3 Hz, H_{12}), 4.0–3.8 (4H, m, $-OC_2H_4O-$), 3.65 (3H, s, –COOMe), 2.6–2.0 (5H, m), 1.9–1.6 (3H, m), 1.4–1.2 (3H, m), 1.36 (3H, s, Me_{19}), 0.91 (3H, s, Me_{20}), 0.89 (3H, d, J=6.9 Hz, Me_{17}); ^{13}C NMR δ: 36.1 (C_1), 107.4 (C_2), 42.9 (C_3), 48.7 (C_4), 132.0 (C_5), 25.1 (C_6), 26.9 (C_7), 35.8 (C_8), 40.6 (C_9), 133.4 (C_{10}), 47.7 (C_{11}), 64.2 (C_{12}), 130.0 (C_{13}), 108.7 (C_{14}), 138.4 (C_{15}), 143.0 (C_{16}), 16.4 (C_{17}), 177.6 (C_{18}), 24.5 (C_{19}), 21.8 (C_{20}), 52.1 (–COO*Me*), 64.6 and 64.3 ($-OC_2H_4O-$); EIMS: 404 (M^+, 1), 293(12), 233(8), 161(5); EIHRMS: calcd for $C_{23}H_{32}O_6$ (M^+) 404.2199, found (M^+) 404.2193.

3.10. Reaction of 16/17 with TPAP: 18

To a mixture of **16/17** (15 mg, 0.037 mmol), *N*-methylmorpholine *N*-oxide (8 mg, 0.061 mmol) and molecular sieves (25 mg) in anhydrous DCM (2 ml), under argon, at room temperature was added TPAP (2 mg, 0.006 mmol). The mixture reaction was stirred for 30 min and then filtered on silica gel (EtOAc), the organic layer was evaporated to yield the expected compound **18** (oil, 15 mg, 99%).

3.10.1. Methyl 15,16-epoxy-2-ethylenedioxy-12-oxo-5(10),13(16),14-*ent*-halimatrien-18-oate (18). $[\alpha]_D^{22}$= −69.5° (*c*=0.90, $CHCl_3$); UV (EtOH): 252, 215, 204 nm; IR (film): 3138, 1728, 1669, 1562, 1510, 1462, 1377, 1240, 1157, 1076, 999, 874 cm^{-1}; ^1H NMR δ: 8.04 (1H, s, H_{16}), 7.39 (1H, s, H_{15}), 6.75 (1H, s, H_{14}), 3.95–3.79 (4H, m, $-OC_2H_4O-$), 3.69 (3H, s, –COOMe), 2.95 and 2.79 (1H, d, J_{AB}=14.4 Hz, H_{11}), 2.36 (1H, d, J=12.5 Hz, H_{3A}), 2.30 (1H, d, J=12.5 Hz, H_{1A}), 2.10 (1H, d, J=12.5 Hz, H_{1B}), 2.1–1.9 (2H, m), 1.7–1.6 (2H, m), 1.3–1.2 (1H, m), 1.58 (1H, d, J=12.5 Hz, H_{3B}), 1.33 (3H, s, Me_{19}), 1.05 (3H, s, Me_{20}), 0.87 (3H, d, J=6.9 Hz, Me_{17}); ^{13}C NMR δ: 36.6 (C_1), 107.2 (C_2), 42.1 (C_3), 48.4 (C_4), 131.9 (C_5), 23.0 (C_6), 25.7 (C_7), 34.0 (C_8), 41.0 (C_9), 129.6 (C_{10}), 48.5 (C_{11}), 194.6 (C_{12}), 129.4 (C_{13}), 108.7 (C_{14}), 143.9 (C_{15}), 147.9 (C_{16}), 15.3 (C_{17}), 177.4 (C_{18}), 24.2 (C_{19}), 21.7 (C_{20}), 51.9 (–COO*Me*), 64.3 and 64.1 ($-OC_2H_4O-$); EIMS: 402 (M^+, 1), 292(100), 233(76), 173(25), 147(15), 95(62), 69(38); EIHRMS: calcd for $C_{23}H_{30}O_6$ (M^+) 402.2042, found (M^+) 402.2048.

3.11. Reaction of 15 with *p*-TsOH: 19

Ketone **15** (24 mg, 0.050 mmol) in acetone (2 ml) was stirred at room temperature in the presence of *p*-toluenesulfonic acid (6 mg, 0.036 mmol) for 5 h. The mixture reaction was diluted with Et_2O and washed successively with a 6% aqueous solution of $NaHCO_3$ and water. The organic layer was dried and evaporated to give a crude which was chromatographed on silica gel (hexane/AcOEt, 8/2) to yield **19** (oil, 16 mg, 72%).

3.11.1. Methyl 15-bromo-13,15-epoxy-2-oxo-16-nor-15-homo-1(12),5(10),13,15-*ent*-halimatetraen-18-oate (19). UV (EtOH): 356, 264, 208 nm; IR (film): 3148, 1732, 1699, 1464, 1431, 1377, 1327, 1269, 1161, 1107, 868,

737 cm^{-1}; ^1H NMR δ: 7.46 (1H, s, H_{15}), 6.52 (1H, s, H_{14}), 3.59 (3H, s, –COOMe), 2.90 and 2.84 (1H, d, J=13.2 Hz, H_{11}), 2.82 and 2.48 (1H, d, J=15.2 Hz, H_3), 2.36 (1H, ddd, J=18.0, 6.2, 1.0 Hz, H_{6A}), 2.20 (1H, ddd, J=18.0, 9.2, 1.0 Hz, H_{6B}), 1.7–1.5 (3H, m), 1.39 (3H, s, Me_{19}), 1.01 (3H, s, Me_{20}), 0.96 (3H, d, J=6.3 Hz, Me_{17}); ^{13}C NMR δ: 130.6 (C_1), 193.4 (C_2), 52.1 (C_3), 49.4 (C_4), 128.1 (C_5), 23.9 (C_6), 27.0 (C_7), 37.0 (C_8), 43.6 (C_9), 149.7 (C_{10}), 49.5 (C_{11}), 132.9 (C_{12}), 147.3 (C_{13}), 103.7 (C_{14}), 116.4 (C_{15a}), 143.5 (C_{15}), 16.3 (C_{17}), 174.4 (C_{18}), 22.5 (C_{19}), 20.2 (C_{20}), 52.3 (–COO*Me*); EIMS: 420 (M^+, 6), 418(6), 339(87), 279(100), 189(82), 69(52), 55(81); EIHRMS: calcd for $C_{21}H_{23}BrO_4$ (M^+) 418.0780, found (M^+) 418.0788.

3.12. Reaction of 18 with *p*-TsOH: chettaphanin II (3)

Ketone **18** (5 mg, 0.012 mmol) in acetone (1.5 ml) was stirred at room temperature in the presence of *p*-toluenesulfonic acid (2 mg, 0.01 mmol) for 5 h. The mixture reaction was diluted with Et_2O and washed successively with a 6% aqueous solution of $NaHCO_3$ and water. The organic layer was dried and evaporated to give a crude orange oil which was chromatographed on silica gel (hexane/AcOEt, 9/1) to yield chettaphanin II **3** (3 mg, 72%).

3.12.1. Chettaphanin II: methyl 15,16-epoxy-2-oxo-1(12),5(10),13(16),14-*ent*-halimatetraen-18-oate (3). Mp: 127°C (Et_2O); $[\alpha]_D^{22}=-435.0°$ (c=0.81, Me_2CO); UV (EtOH): 356, 264, 208 nm; IR (film): 3163, 1728, 1682, 1574, 1464, 1433, 1377, 1265, 1167, 1109, 1017 cm^{-1}; ^1H NMR δ: 8.57 (1H, s, H_{16}), 7.43 (1H, s, H_{15}), 7.00 (1H, s, H_{14}), 3.57 (3H, s, COOMe), 2.81 and 2.45 (1H, d, J=15.7 Hz, H_3), 2.71 and 2.66 (1H, d, J=16.9 Hz, H_{11}), 2.37 (1H, ddd, J=18.0, 6.2, 1.0 Hz, H_{6A}), 2.25 (1H, ddd, J=18.0, 9.2, 1.0 Hz, H_{6B}), 1.66–1.58 (2H, m, H_7), 1.59–1.56 (1H, m, H_8), 1.38 (3H, s, Me_{19}), 0.99 (3H, s, Me_{20}), 0.97 (3H, d, J=6.2 Hz, Me_{17}); ^{13}C NMR δ: 127.9 (C_1), 195.1 (C_2), 52.1 (C_3), 48.4 (C_4), 125.1 (C_5), 23.7 (C_6), 27.0 (C_7), 37.1 (C_8), 42.4 (C_9), 150.3 (C_{10}), 50.3 (C_{11}), 139.7 (C_{12}), 121.8 (C_{13}), 111.0 (C_{14}), 142.7 (C_{15}), 146.3 (C_{16}), 16.4 (C_{17}), 174.6 (C_{18}), 22.3 (C_{19}), 20.3 (C_{20}), 52.3 (–COO*Me*); EIMS: 340 (M^+, 35), 281(100), 256(18), 205(17), 152(10), 105(18), 91(19), 69(32); EIHRMS: calcd for $C_{21}H_{24}O_4$ (M^+) 340.1674, found (M^+) 340.1668.

3.13. Successive reactions of protection, reduction and protection starting from 6: 20

To a solution of **6** (175 mg, 0.55 mmol) in ethylene glycol (0.5 ml), was added benzene (5 ml) and was refluxed in the presence of *p*-toluenesulfonic acid (5 mg, 0.02 mmol) for 8 h. The mixture was extracted with Et_2O and washed with a 6% aqueous solution of $NaHCO_3$ and water. Evaporation of the solvent yielded a crude (200 mg, 0.49 mmol, 90%) which was dissolved in Et_2O (4 ml) and was added LAH (20 mg, 0.40 mmol). The mixture was stirred for 1.5 h at room temperature and quenched by addition of AcOEt sat. Evaporation of the solvent yielded a crude (185 mg, 0.48 mmol, 97%), which was dissolved in DMM (1 ml). To the solution was added BrLi (0.1 mg, 1.20 mmol) and *p*-toluenesulfonic acid (1 mg, 0.005 mmol) and was stirred for 12 h at room temperature. The reaction mixture was then treated with NaCl sat., extracted with Et_2O and washed with a 6% aqueous solution of $NaHCO_3$ and water. Evaporation followed by chromatography on silica gel yielded the desired compound **20** (oil, 200 mg, 97%).

3.13.1. 2,13-Diethylendioxy-18-methoxymethylenoxy-14,15-dinor-5(10)-*ent*-halimene (20). $[\alpha]_D^{22}=+34.9°$ (c=1.37, $CHCl_3$); IR (film): 1466, 1381, 1148, 1107, 1078, 1047 cm^{-1}; ^1H NMR δ: 4.57–4.56 (2H, m, MeOCH_2-O–), 3.95–3.91 (8H, m, –OC_2H_4O–), 3.44 and 3.17 (1H, d, J_{AB}=9.0 Hz, H_{18}), 3.33 (3H, s, *Me*OCH_2O–), 2.20 (2H, s, H_1), 2.18–2.04 (3H, m), 2.00 and 1.51 (1H, d, J_{AB}=13.4 Hz, H_3), 1.8–1.7 (2H, m), 1.6–1.3 (4H, m), 1.29 (3H, s, Me_{16}), 1.09 (3H, s, Me_{19}), 0.85 (3H, s, Me_{20}), 0.84 (3H, d, J=6.2 Hz, Me_{17}); ^{13}C NMR δ: 35.2 (C_1), 108.9 (C_2), 40.1 (C_3), 41.5 (C_4), 133.0 (C_5), 25.0 (C_6), 33.1 (C_7), 33.6 (C_8), 40.5 (C_9), 132.5 (C_{10}), 29.9 (C_{11}), 27.0 (C_{12}), 110.4 (C_{13}), 23.7 (C_{16}), 16.1 (C_{17}), 74.8 (C_{18}), 23.2 (C_{19}), 20.7 (C_{20}), 55.2 (*Me*OCH_2O–), 96.7 (MeOCH_2O–), 64.5 and 63.9 (–OC_2H_4O–); EIMS: 424 (M^+, 20), 287(48), 243(33), 165(25), 115(26), 87 (100); EIHRMS: calcd for $C_{24}H_{40}O_6$ (M^+) 424.2825, found (M^+) 424.2829.

3.14. Reaction of 20 with *m*-CPBA: 21

To a solution of **20** (188 mg, 0.44 mmol) in DCM (0.8 ml) at 0°C, was added *m*-CPBA (150 mg, 0.88 mmol) dissolved in DCM (2.2 ml). The reaction mixture was stirred for 30 min at room temperature and then treated with a 6% aqueous solution of Na_2SO_3. Extraction with AcOEt, followed by successive washing of the organic layer with a 10% aqueous Na_2SO_3 solution, 6% aqueous $NaHCO_3$ solution and water. The organic layer was dried and evaporated. Purification by chromatography on silica gel yielded desired compound **21** (171 mg, 86%).

3.14.1. 5α,10α-Epoxy-2,13-diethylendioxy-18-methoxymethylenoxy-14,15-dinor-*ent*-halimane (21). $[\alpha]_D^{22}=+9.3°$ (c=1.29, $CHCl_3$); IR (film): 1466, 1373, 1213, 1148, 1111, 1047, 949, 858 cm^{-1}; ^1H NMR δ: 4.64 and 4.60 (1H, d, J_{AB}=6.7 Hz, MeOCH_2O–), 4.66 and 3.93 (8H, m, –OC_2H_4O–), 3.60 and 3.28 (1H, d, J=9.2 Hz, H_{18}), 3.37 (3H, s, *Me*OCH_2O–), 2.25 and 2.09 (1H, d, J_{AB}=15 Hz, H_1), 1.98–1.95 (1H, m, H_6), 1.85 and 1.38 (1H, d, J_{AB}=13.6 Hz, H_3), 1.8–1.2 (8H, m), 1.30 (3H, s, Me_{16}), 1.04 (3H, s, Me_{19}), 0.86 (3H, s, Me_{20}), 0.76 (3H, d, J=6.2 Hz, Me_{17}); ^{13}C NMR δ: 35.4 (C_1), 108.1 (C_2), 38.2 (C_3), 39.3 (C_4), 67.9 (C_5), 25.9 (C_6), 24.7 (C_7), 34.0 (C_8), 38.9 (C_9), 68.8 (C_{10}), 31.2 (C_{11}), 33.1 (C_{12}), 110.2 (C_{13}), 24.0 (C_{16}), 16.4 (C_{17}), 73.5 (C_{18}), 20.9 (C_{19}), 18.1 (C_{20}), 55.4 (*Me*OCH_2O–), 96.9 (MeOCH_2O–), 64.7, 64.5 and 63.4 (–OC_2H_4O–); EIMS: 440 (M^+, 1), 187(20), 126(15), 87(100).

3.15. Reaction of 21 with *p*-TsOH: 22

To a solution of **21** (132 mg, 0.30 mmol) in distilled acetone over $KMnO_4$ (4 ml), was added *p*-toluenesulfonic acid (5 mg). The reaction mixture was stirred for 2 h and was extracted with AcOEt followed by successive washing of the organic layer with 6% aqueous $NaHCO_3$ solution and water. The organic layer was dried and evaporated to give a

crude mixture which was chromatographed on silica gel to yield the expected compound **22** (oil, 68 mg, 64%).

3.15.1. 5α-Hydroxy-18-methoxymethylenoxy-14,15-dinor-1(10)-*ent*-halimen-2,13-dione (22). $[\alpha]_D^{22}=-9.6°$ (c=0.5, $CHCl_3$); IR (film): 3474, 1717, 1669, 1464, 1370, 1150, 1107, 1044, 918. cm^{-1}; ^1H NMR δ: 5.90 (1H, s, H_1), 4.53 and 4.50 (1H, d, J_{AB}=6.6 Hz, MeOCH_2O–), 3.39 and 3.38 (1H, d, J_{AB}=9.6 Hz, H_{18}), 3.29 (3H, s, *Me*OCH_2O–), 2.56 and 2.37 (1H, d, J_{AB}=16.6 Hz, H_3), 2.35–2.30 (2H, m, H_{12}), 2.12 (3H, s, Me_{16}), 2.0–1.8 (5H, m), 1.6–1.4 (2H, m), 1.18 (3H, s, Me_{20}), 1.10 (3H, s, Me_{19}), 0.91 (3H, d, J=6.6 Hz, Me_{17}); ^1H NMR (DMSO) δ: 5.71 (1H, s, H_1), 4.77 (1H, s, –OH), 4.47 and 4.45 (1H, d, J_{AB}=6.6 Hz, MeOCH_2O–), 3.34 and 3.25 (1H, d, J_{AB}=9.6 Hz, H_{18}), 3.16 (3H, s, *Me*OCH_2O), 2.62 and 2.13 (1H, d, J_{AB}=16.6 Hz, H_3), 2.36 and 2.20 (1H, m, H_{12}), 2.05 (3H, s, Me_{16}), 1.75 and 1.37 (1H, m, H_6), 1.66 (2H, m, H_{11}), 1.48 (1H, m, H_8), 1.23 (2H, m, H_7), 1.10 (3H, s, Me_{20}), 0.95 (3H, s, Me_{19}), 0.84 (3H, d, J=6.3 Hz, Me_{17}); ^{13}C NMR δ: 126.9 (C_1), 199.7 (C_2), 44.5 (C_3), 45.6 (C_4), 74.4 (C_5), 31.3 (C_6), 26.0 (C_7), 37.0 (C_8), 44.3 (C_9), 167.9 (C_{10}), 32.8 (C_{11}), 39.2 (C_{12}), 208.9 (C_{13}), 31.0 (C_{16}), 17.0 (C_{17}), 73.7 (C_{18}), 20.2 (C_{19}), 26.5 (C_{20}), 56.4 (*Me*OCH_2O–), 97.6 (MeOCH_2O–); ^{13}C NMR (DMSO) δ: 124.9 (C_1), 192.2 (C_2), 42.9 (C_3), 44.3 (C_4), 71.3 (C_5), 30.6 (C_6), 24.7 (C_7), 34.6 (C_8), 42.6 (C_9), 166.7 (C_{10}), 29.8 (C_{11}), 37.8 (C_{12}), 208.0 (C_{13}), 19.8 (C_{16}), 16.1 (C_{17}), 72.13 (C_{18}), 19.2 (C_{19}), 26.1 (C_{20}), 95.9 (MeOCH_2O–), 54.6 (*Me*OCH_2O); EIMS: 352 (M^+, 5), 307(10), 282(11), 235(20), 189(13), 165(100), 137(28); EIHRMS: calcd for $C_{20}H_{32}O_5$ $(M)^+$ 352.2250, found (M^+) 352.2258.

3.16. Reaction of 18 with *m*-CPBA: 23

To a solution of **18** (31 mg, 0.077 mmol) in DCM (0.1 ml) at 0°C, was added *m*-CPBA (15.9 mg, 0.092 mmol) dissolved in DCM (0.18 ml). The reaction mixture was stirred for 12 h at room temperature and then treated with a 6% aqueous solution of Na_2SO_3. Extraction with AcOEt, followed by successive washing of the organic layer with a 10% aqueous Na_2SO_3 solution, 6% aqueous $NaHCO_3$ solution and water. The organic layer was dried and evaporated to yield the expected compound **23** (29 mg, 92%).

3.16.1. Methyl 5α,10α-15,16-diepoxy-2-ethylendioxy-12-oxo-13(16),14-*ent*-halimandien-18-oate (23). $[\alpha]_D^{22}=-23.6°$ (c=0.5, $CHCl_3$); IR (film): 1732, 1670, 1561, 1508, 1458, 1375, 1157, 1123, 1044, 874 cm^{-1}; ^1H NMR δ: 8.08 (1H, t, J=1.0 Hz, H_{16}), 7.42 (1H, t, J=1.0 Hz, H_{15}), 6.77 (1H, t, J=1.0 Hz, H_{14}), 3.88–3.84 (4H, m, –OC_2H_4O–), 3.78 (3H, s, –COOMe), 3.21 and 2.77 (1H, d, J_{AB}=15.7 Hz, H_{11}), 2.14 (2H, s, H_1), 2.01 and 1.68 (1H, d, J_{AB}=13.6 Hz, H_3), 2.0–1.9 (2H, m), 1.6–1.5 (2H, m), 1.4–1.3 (1H, m), 1.31 (3H, s, Me_{19}), 1.18 (3H, s, Me_{20}), 0.96 (3H, d, J=7 Hz, Me_{17}); ^{13}C NMR δ: 36.6 (C_1), 106.4 (C_2), 40.0 (C_3), 47.4 (C_4), 66.2 (C_5), 24.3 (C_6), 24.0 (C_7), 33.5 (C_8), 39.6 (C_9), 68.9 (C_{10}), 46.61 (C_{11}), 194.1 (C_{12}), 129.3 (C_{13}), 108.7 (C_{14}), 144.1 (C_{15}), 147.3 (C_{16}), 15.9 (C_{17}), 176.0 (C_{18}), 20.8 (C_{19}), 19.3 (C_{20}), 51.8 (–COO*Me*), 64.1–64.1 (–OC_2H_4O–); EIMS: 418 (M^+, 4), 292(30), 233(18), 146(48), 95(62), 95(50); EIHRMS: calcd for $C_{23}H_{30}O_7$ $(M)^+$ 418.1991, found (M^+) 418.1998.

3.17. Reaction of 23 with $HClO_4$: 24, 25 and chettaphanin I (2)

To a solution of **23** (41 mg, 0.098 mmol) in DMF (1.5 ml) $HClO_4$ 63% (0.025 ml) was added. The mixture reaction was stirred for 3 h and then water was added. Extraction with Et_2O followed by washing with water. The organic layer was dried and evaporated to give a crude oil which was chromatographed on silica gel to yield **24** (13 mg, 35%), **25** (11 mg, 30%) and chettaphanin I **2** (11 mg, 30%).

3.17.1. Methyl 5α,10α-epoxy-2,12-dioxo-13(16),14-*ent*-halimandien-18-oate (24). $[\alpha]_D^{22}=-35.2°$ (c=0.5, $CHCl_3$); IR (film): 1728, 1680, 1561, 1508, 1458, 1285, 1155, 1045, 874, 667 cm^{-1}; ^1H NMR δ: 7.98 (1H, s, H_{16}), 7.42 (1H, s, H_{15}), 6.68 (1H, s, H_{14}), 3.87 (3H, s, –COOMe), 3.00 and 2.69 (1H, d, J_{AB}=18.6 Hz, H_{11}), 2.73 and 2.70 (1H, d, J_{AB}=17.6 Hz, H_1), 2.46 and 2.27 (1H, d, J=17.6 Hz, H_3), 1.8–1.2 (5H, m), 1.40 (3H, s, Me_{19}), 0.92 (3H, s, Me_{20}), 0.86 (3H, d, J=5.2 Hz, Me_{17}); EIMS: 375 (M^++1, 5), 265(63), 233 (11), 164 (43), 95 (100).

3.17.2. Methyl (10*S*,12*S*)-10,12-15,16-diepoxy-5α,12-hydroxy-2-oxo-13(16),14-*ent*-halimandien-18-oate (25). IR (film): 3400, 1726, 1464, 1196, 1127, 1053, 1009, 972, 665 cm^{-1}; ^1H NMR δ: 7.34 (2H, s, H_{15} and H_{16}), 6.23 (1H, s, H_{14}), 3.57 (3H, s, –COOMe), 2.99 and 2.94 (1H, d, J=12.5 Hz, H_1), 2.8–2.7 (1H, m, H_6), 2.69 and 2.63 (1H, d, J=12.4 Hz, H_3), 2.30 and 2.13 (1H, d, J_{AB}=13.5 Hz, H_{11}), 1.85–1.75 (1H, m, H_6), 1.97–1.85 (1H, m, H_7), 1.70–1.63 (1H, m, H_7), 1.60–1.50 (1H, m, H_8), 1.29 (3H, s, Me_{19}), 0.95 (3H, s, Me_{20}), 0.72 (3H, d, J=6.7 Hz, Me_{17}); ^{13}C NMR δ: 45.9 (C_1), 208.5 (C_2), 47.0 (C_3), 52.8 (C_4), 75.3 (C_5), 29.8 (C_6), 25.0 (C_7), 34.9 (C_8), 48.8 (C_9), 90.4 (C_{10}), 51.7 (C_{11}), 105.4 (C_{12}), 129.1 (C_{13}), 108.6 (C_{14}), 141.0 (C_{15}), 143.4 (C_{16}), 16.7 (C_{17}), 175.1 (C_{18}), 21.9 (C_{19}), 15.0 (C_{20}), 52.1 (–COO*Me*); EIMS: 375 (M^++1, 10), 256(8), 149(38); EIHRMS: calcd for $C_{21}H_{28}O_7$ (M^+) 392.1835, found (M^+) 392.1841.

3.17.3. Chettaphanin I: methyl 15,16-epoxy-5α-hydroxy-2,12-dioxo-1(10),13(16),14-*ent*-halimantrien-18-oate (2). $[\alpha]_D^{22}=-31.7°$ (c=0.3, $CHCl_3$); UV (EtOH): 245 nm; IR (film): 3400, 1728, 1682, 1458, 1377, 1277, 1155, 1121, 1044, 999 cm^{-1}; ^1H NMR δ: 7.98 (1H, s, H_{16}), 7.41 (1H, s, H_{15}), 6.64 (1H, s, H_{14}), 5.84 (1H, s, H_1), 3.71 (3H, s, –COOMe), 3.25 and 3.14 (1H, d, J_{AB}=18.0 Hz, H_{11}), 2.69 and 2.57 (1H, d, J_{AB}=17.4 Hz, H_3), 2.40 (1H, ddd, J=14.0, 14.0, 3.6 Hz, H_{6A}), 2.00 (1H, ddd, J=14.0, 3.0, 3.0 Hz, H_{6B}), 1.8–1.5 (2H, m), 1.3–1.2 (1H, m), 1.38 (3H, s, Me_{19}), 1.20 (3H, s, Me_{20}), 0.89 (3H, d, J=6.8 Hz, Me_{17}); ^1H NMR (DMSO) δ: 8.57 (1H, s, H_{16}), 7.73 (1H, s, H_{15}), 6.68 (1H, s, H_{14}), 5.75 (1H, s, H_1), 5.01 (1H, s, –OH), 3.54 (3H, s, –COOMe), 3.50 and 3.11 (1H, d, J_{AB}=18.0 Hz, H_{11}), 2.60 and 2.21 (1H, d, J_{AB}=17.4 Hz, H_3), 2.2–1.9 (2H, m), 1.7–1.5 (2H, m), 1.3–1.2 (1H, m), 1.20 (3H, s, Me_{19}), 1.10 (3H, s, Me_{20}), 0.82 (3H, d, J=6.8 Hz, Me_{17}); ^{13}C NMR δ: 125.6 (C_1), 197.6 (C_2), 43.2 (C_3), 52.9 (C_4), 72.7 (C_5), 31.8 (C_6), 25.0 (C_7), 35.2 (C_8), 41.2 (C_9), 167.4 (C_{10}), 47.8 (C_{11}), 190.8 (C_{12}), 127.6 (C_{13}), 108.3 (C_{14}), 144.1 (C_{15}), 146.3 (C_{16}), 16.7 (C_{17}), 174.5 (C_{18}), 19.4 (C_{19}), 25.9 (C_{20}), 52.4 (–COO*Me*); EIMS: 374 (M^+, 1), 149 (10), 99(35), 71(52),

57(100); EIHRMS: calcd for $C_{21}H_{26}O_6$ (M^+) 374.1729, found (M^+) 374.1734.

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