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Ring-Opening Aminolysis of Sesquiterpene Lactones: An Easy Entry to Bioactive Sesquiterpene Derivatives. Synthesis of (+)-β-Cyperone and (-)-Eudesma-3,5-diene from Santonin.

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Abstract: Santonin (**1**) and other sesquiterpene lactones (**2-3**) react with pyrrolidine and other cyclic secondary amines to afford γ-hydroxyamides, which by elimination with mesyl chloride in pyridine-benzene at 80°C give unsaturated amides **4a-4c**, **5a-5c** and **6**.
Starting from amides **5a-5c** a series of bioactive compounds against *Locusta migratoria* have been prepared, differing in the oxidation states of the C-3 and C-12 carbon atoms.
Starting from amides **5a** and **6** two conjugated diene eudesmanes (+)-β-cyperone (**15**) and (-)eudesma-3,5-diene (**19**) have been prepared involving an elaboration of the amide group of the side chain of the eudesmane skeleton. Copyright © 1996 Elsevier Science Ltd

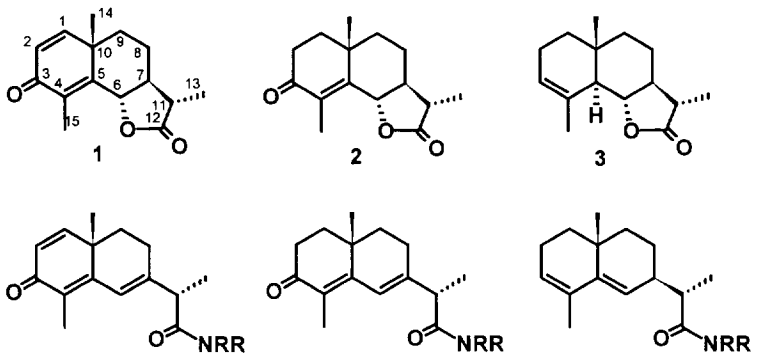
As part of our current synthetic programme related to natural sesquiterpenes with biological activity, we have previously described an easy non-catalyzed ring-opening aminolysis of several sesquiterpene lactones.[1] For example, santonin (**1**) and lactones **2** and **3**, which are easily prepared from the former, react cleanly with pyrrolidine at room temperature to afford the corresponding γ-hydroxyalkylamides, which by elimination give the unsaturated amides **4a**, **5a** and **6** respectively.

These sesquiterpene amides are very interesting products because compounds **4a** and **5a** and other of related structure are active as inhibitors of the biosynthesis of the juvenile hormone *in vitro* and produce alterations in the nymphs of *Locusta migratoria,* a pest of the agriculture in the North-African countries.[2] Furthermore, after removal of the pyrrolidine group compounds **5a** and **6** are useful intermediates in the synthesis of other sesquiterpenes with a conjugated diene system between the C-4–C-7 and the C-3–C-6 positions respectively.

RESULTS AND DISCUSSION

In this paper we wish to report in full the outcome of our investigation on the ring-opening aminolysis of lactones **1**, **2** and **3** to prepare the corresponding unsaturated sesquiterpene amides **4a-4c**, **5a-5c** and **6.** Compounds **4a**, **5a-5c** are bioactive[2-3] against *L. migratoria* and besides **5a-5c** are useful starting materials to synthesize other bioactive[3] sesquiterpene derivatives **7a-7c**, **8a-8c** and **9a-9c**.

On the other hand the unsaturated amides **5a** and **6** so obtained are also useful starting materials for the synthesis of conjugated diene eudesmanes such as (+)-β-cyperone (**15**) and (-)-eudesma-3,5-diene (**19**). These syntheses include as key step the reductive removal of the amide group to the hydroxy derivatives **13** and **16**.



4a RR = -$(CH_2)_4$- **5a** RR = -$(CH_2)_4$- **6** RR = -$(CH_2)_4$-

4b RR = -$(CH_2)_5$- **5b** RR = -$(CH_2)_5$-

4c RR = -$CH_2)_2O(CH_2)_2$- **5c** RR = -$CH_2)_2O(CH_2)_2$-

A) Ring-opening aminolysis of sesquiterpene lactones **1**, **2** *and* **3**.

The aminolysis of lactones requires generally long reaction times at high temperatures when amines[4-5] are used as nucleophiles, and although metallic (Li, Al, Sn) amides[6-8] are useful reagents to carry out this reaction, they are not compatible with sensitive functionalities. Recently, an aluminium chloride mediated aminolysis of 5-7 membered lactones has been reported.[9]

We found that the aminolysis of sesquiterpene lactones, such us **1**, **2**, and **3**, was conveniently carried out in benzene and excess of pyrrolidine at room temperature. The reaction was performed by adding 20 eq. of pyrrolidine to a solution of lactone in benzene and stirring at room temperature for the time indicated in Table 1. The product was isolated by evaporation of the solvent and the excess of amine. As Table 1 shows, the reaction with pyrrolidine is quantitative at room temperature, while morpholine and piperidine need higher temperatures. The facility of the ring-opening aminolysis reaction seems to be determined by steric factors rather than electronic factors. Thus, whilst the less hindered cyclic secondary amines, including the lower basicity morpholine react with santonin (**1**) and dihydrosantonin (**2**) in the conditions indicated, acyclic secondary amines did not react.[1]

Table 1. Aminolysis-Elimination of Sesquiterpene lactones **1**, **2** and **3**.

AMINOLYSIS					ELIMINATION		
Substrate	Amine	T(°C)	t(h)	Yield[a]	t(h)	**Product**	Overall Yield[b]
1	pyrrolidine	rt	3.5	100	5.5	**4a**	78
1	piperidine	60	36	92(8)	7	**4b**	57(34)
1	morpholine	60	36	69(31)	7	**4c**	24(60)
2	pyrrolidine	rt	4	100	5.5	**5a**	78
2	piperidine	60	36	93(7)	7	**5b**	58(28)
2	morpholine	60	36	75(25)	7	**5c**	34(50)
3	pyrrolidine	rt	4	100	5.5	**6**	65(22)

[a]Unreacted lactone in parenthesis (by ^{1}H NMR).

[b]Recovered lactone in parenthesis (isolated).

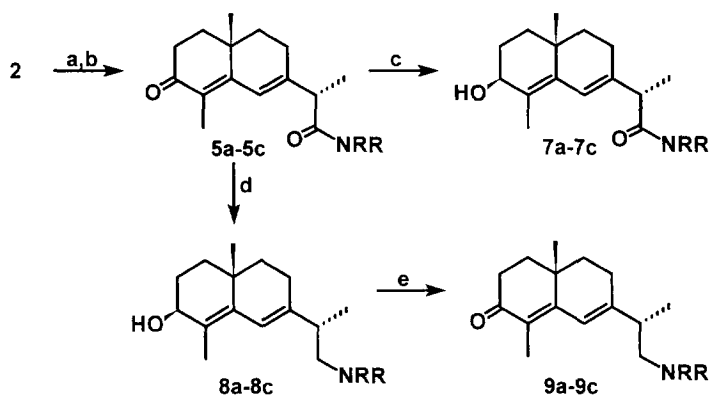
The elimination of the resulting hydroxyl group at C-6 was achieved with excess of mesyl chloride in pyridine-benzene at 80°C giving good yields of the unsaturated amides, especially with pyrrolidine hydroxyamides. Relactonization was observed to some extent with other hydroxyamides.

In conclusion, sesquiterpene lactones **1**, **2** and **3** react cleanly with cyclic secondary amines, in particular pyrrolidine, at room temperature to afford γ-hydroxyamides, which by elimination with mesyl chloride in pyridine-benzene at 80°C give the unsaturated amides **4a**, **5a** and **6**, respectively.

B) Synthesis of some sesquiterpene derivatives bioactive against Locusta migratoria.

We have already reported on the *in vitro* inhibition of the juvenile hormone biosynthesis of *Locusta migratoria* by compounds **4a** and **5a**.[2] Now, in order to check the influence of the different functionalities present in them we have prepared a series of new derivatives of the aminolysis-elimination products **5a-5c**. These derivatives have been prepared by modifying the oxidation states of the C-3 and C-12 carbon atoms.

So, by selective reduction of the ketone carbonyl group on C-3 with $NaBH_4/CeCl_3$, we obtained good yields (*ca.* 90%) of the corresponding 3β-alcohols **7a-7c**. On the other hand, a more energetic reduction with $LiAlH_4$ allowed us to reduce simultaneously the ketone carbonyl on C-3 and the amide carbonyl group on C-12 obtaining the corresponding 3β-alcohol-12-amine compounds **8a-8c** (*ca.* 90% yield). Finally oxidation of the allylic hydroxyl group with MnO_2 afforded compounds **9a-9c** (*ca.* 80% yield).



Reagents: (a) R_2NH; (b) MsCl, pyr; (c) $NaBH_4$, $CeCl_3$; (d) $LiAlH_4$; (e) MnO_2

To sum up, we have prepared thirteen sesquiterpene derivatives with the following combination of oxidation states on the C-3 and C-12 carbon atoms: ketone-amide (**4a** and **5a-5c**), alcohol-amide (**7a-7c**), alcohol-amine (**8a-8c**) and ketone-amine (**9a-9c**). All the sesquiterpene derivatives with the amide group on C-12, as well as ketone-alcohol **13** (see later on), shown a remarkable action as inhibitors of juvenile hormone biosynthesis in the *corpora allata* of *Locusta migratoria*.[3] Detailed results on the inhibition of juvenile hormone biosynthesis will be published elsewhere.

C) Synthesis of (+)-β-cyperone (**15**) *and (-)-eudesma-3,5-diene* (**19**)

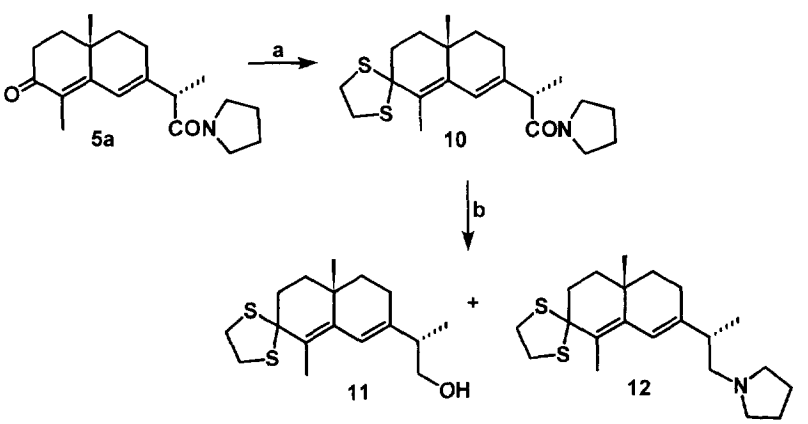
The conjugated diene systems between the C-4–C-7 or C-3–C-6 positions are present in a number of naturally occurring sesquiterpenes. Here we wish to report on the synthesis of (+)-β-cyperone (**15**) and (-)-eudesma-3,5-diene (**19**) starting from the unsaturated amides **5a** and **6** respectively. (+)-β-Cyperone (**15**) is a well known compound that has been synthesized from different starting materials.[10,11] Ourisson *et al.* reported

its synthesis from santonin (**1**) through a photochemical key step.[12] Compound **19** is the C-10 epimer of a natural product isolated for the first time from *Ursinia trifida*.[13]

For the synthesis of both compounds we needed to remove the pyrrolidine group. Some trials of nucleophilic substitution, including the use of microwaves[14] and activation of the amide group,[15] were unsuccessful and therefore we looked into reductive methods.

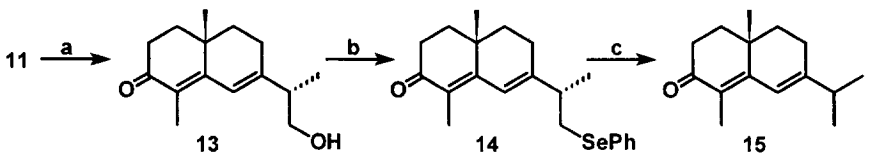
In recent years, two methods have been reported for the transformation of simple *N,N*-disubstituted carboxamides to the corresponding oxygenated derivatives (alcohol or aldehyde) with good yields. Gyoung *et al.*[16] have reported a convenient procedure using a 1M solution of $LiAlH_4$ followed by quenching the reaction mixture with aqueous $NaBH_4$ which gives good yields of the corresponding alcohols. Later, Cha[17] used a new derivative of $LiAlH_4$, lithium tripiperidinoaluminum hydride (LTPDA) easily prepared from $LiAlH_4$ and piperidine, which affords the corresponding aldehydes.

In order to test these reductive methods, compound **10**, in which the carbonyl group on C-3 is protected as a thioketal, was prepared by reaction of **5a** with ethanedithiol in AcOH-BF_3.Et_2O. Several reduction experiments with a 1M THF solution of $LiAlH_4$, varying the hydride equivalents, the temperature and the reaction times, were carried out. The best results were obtained at 0°C with 3 eq. of hydride for 30 min. (26% of compound **11**, 34% of **12**, ratio **11**:**12** 1:1.3). As the results were unsuccessful from the synthetic point of view we looked on the Cha method. The first trials of reduction of **10**, which were carried out by quenching the reaction mixture with aqueous NH_4Cl, showed the presence of alcohol **11**, the corresponding aldehyde and amine **12**. In the following trials, in order to obtain only **11** and **12**, the reaction mixture was quenched with aq. $NaBH_4$. We got acceptable results with a recently prepared solution of LTPDA (16 eq. of hydride, at 0°C for 2 h 15 min): 53% yield of alcohol **11**, 22% yield of amine **12** and 11% of recovered unreacted starting material **10**, with a great improvement on the ratio **11**:**12** (1:0.4).



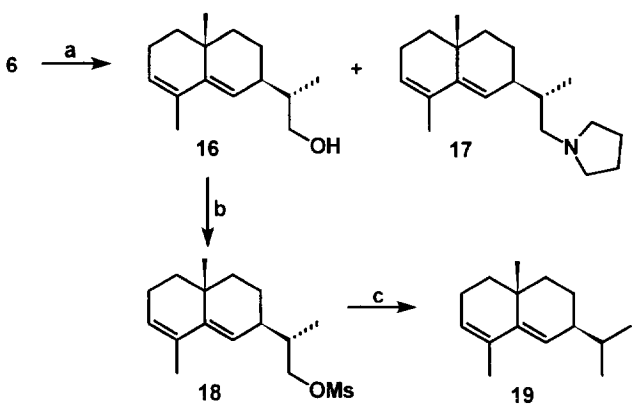
Reagents: (a) $HSCH_2CH_2SH$, AcOH, $BF_3{\cdot}Et_2O$; (b) LTPDA, THF.

With alcohol **11** in our hands, we thought to carry out the reduction of the hydroxyl group on C-12 through the corresponding phenylselenide, in order to get the isopropyl unit present in (+)-β-cyperone. Starting from **11**, the thioketal ring was cleaved with periodic acid in CH_2Cl_2-MeOH-H_2O at room temperature for 10 min yielding **13** (75%). Next, we carried out the substitution of the hydroxyl group by a phenylselenide group by treatment with *N*-phenylselenophthalimide/tri-*n*-butylphosphine (NPSP-Bu_3P), obtaining **14** in a 60% yield. Finally, reductive removal of the phenylseleno group with Raney Nickel gave (+)-β-cyperone (**15**) in quantitative yield (25% overall yield from **5a**). The spectroscopic features of the synthetic product were fully consistent with the structure **15** and identical to literature data.[18]



Reagents: (a) H_5IO_6; (b) NPSP, *n*-Bu_3P ; (c) Raney Ni.

In a similar way starting from **6** we prepared compound **19**. The reduction of the amide group presented further difficulties as compound **19** showed a remarkable lesser reactivity and a significant part of the starting material was recovered unaltered. The best results, with lithium tripiperidinoaluminum hydride (LTPDA) (8 eq, at 0°C for 2 h 20 min), afforded a 23% yield of alcohol **16** (43% on consumed starting material), 10% of the amine **17** and 47% of unreacted **6**, with a similar alcohol-amine ratio to that obtained in the reduction of compound **10** (ratio **16**:**17**, 1:0.45).



Reagents: (a) LTPDA, THF; (b) MsCl, Et_3N; (c) $LiHBEt_3$.

The reduction of the 12-hydroxyl group was carried out by a different procedure. Treatment of the mesylate derivative **18** with lithium triethylborohydride yielded compound **19** in good yield (76%, two steps). The spectroscopic data (^1H NMR, ^{13}C NMR, MS) are fully consistent with structure **19** and its synthesis from **6** was achieved with an overall yield of 32%.

EXPERIMENTAL

Melting points were determined in capillary tubes with a Büchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 281 spectrometer, as liquid films for oils and in KBr disk for solids. NMR spectra were run on a Brucker AC-200 instrument (200.1 MHz for ^1H and 50.3 MHz for ^{13}C) or a Varian Unity 400 (399.95 MHz for ^1H and 100.58 MHz for ^{13}C) in $CDCl_3$ solutions. The carbon type (methyl,

methylene, methine, or quaternary) was determined by DEPT experiments. Heteronuclear ^{1}H-^{13}C correlation experiments (HMQC) were performed for compounds **6**, **10**, **16** and **19**. Mass spectra were recorded at 70 eV. Optical rotations were determined on a Polartronic D (Schmidt and Haensch) polarimeter as solutions in $CHCl_3$. Flash chromatography was carried out on SDS Chromagel 60 silica gel.

General procedure for aminolysis-elimination of sesquiterpene lactones **1**, **2** *and* **3**.

A solution of sesquiterpene lactone (2 mmol) in benzene (6 mL) and amine (40 mmol, 3.33 mL when it is pyrrolidine) was stirred at the indicated temperature and for the indicated time in Table 1. After this time the solvent and excess of amine were evaporated at reduced pressure to give the corresponding hydroxyamide. To the obtained residue dissolved in benzene (5 mL) and pyridine (5 mL) at 0°C under argon it was added MsCl (3 mL, 38 mmol) and the mixture was heated at 80°C. After stirring at this temperature for the indicated time in Table 1, the mixture was poured on 2M HCl and extracted with EtOAc. The organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Filtration and solvent removal followed by flash chromatography on silica gel eluting with mixtures of hexane-EtOAc gave the unsaturated amide.

1-[(11S)-3-Oxoeudesma-1,4,6-trien-12-oyl]-pyrrolidine (**4a**): yield: 78%; pale yellow solid, m.p. 79-82°C (Hexane-EtOAc); $[\alpha]_D^{26}$ +357° (*c* 1.28); MS *m/e* 300 (M^++1, 75), 299 (M^+, 75), 284 (35), 201 (19), 98 (100); HRMS 300.1961, $C_{19}H_{26}NO_2$ required 300.1957; IR ν_{max} 1645-1640, 1609, 831 cm^{-1}; ^1H NMR (200 MHz) δ 6.70 (d, J = 9.8 Hz, 1H, H-1), 6.48 (brd, J = 1.8 Hz, 1H, H-6), 6.21 (d, J = 9.8 Hz, 1H, H-2), 3.5-3.3 (m, 4H, 2C***H***$_2$N), 3.36 (q, J = 7.0 Hz, 1H, H-11), 2.43 (dddd, J = 1.8, 5.6, 11.0, 18.0 Hz, 1H, H-8), 2.26 (brddd, J = 1.6, 6.6, 18.0 Hz, 1H, H-8′), 1.92 (brs, 3H, H-15), 2.0-1.8 (m, 4H, 2C***H***$_2$CH$_2$N), 1.75 (ddd, J = 1.6, 5.6, 13.0 Hz, 1H, H-9β), 1.54 (ddd, J = 6.6, 11.0, 13.0 Hz, 1H, H-9α), 1.33 (d, J = 7.0 Hz, 3H, H-13), 1.14 (s, 3H, H-14); ^{13}C NMR (50.3 MHz) δ 186.5 (C-3), 170.7 (C-12), 154.7 (C-1), 153.5, 145.9, 128.2 (C-4, C-5, C-7), 126.9 (C-2), 121.6 (C-6), 46.4, 46.0 (2***C***H$_2$N), 46.3 (C-11), 37.3 (C-10), 31.9 (C-9), 26.0 (C-8), 25.0 (C-14), 24.0, 23.6 (2***C***H$_2$CH$_2$N), 16.4 (C-13), 9.9 (C-15).

1-[(11S)-3-Oxoeudesma-1,4,6-trien-12-oyl]-piperidine (**4b**): yield: 57% (recovered santonin 34%); yellow oil, ; $[\alpha]_D^{21}$ +227° (*c* 1.6); MS *m/e* 313 (M^+, 60), 298 (24), 201 (13), 113 (5), 112 (100); HRMS 313.2033, $C_{20}H_{27}NO_2$ required 313.2035; IR ν_{max} 3640-3160, 1680, 1620, 840 cm^{-1}; ^1H NMR (200 MHz) δ 6.71 (d, J = 9.9 Hz, 1H, H-1), 6.48 (brs, 1H, H-6), 6.23 (d, J = 9.9 Hz, 1H, H-2), 3.8-3.7 (m, 1H, C***H***$_2$N), 3.50 (q, J = 6.7 Hz, 1H, H-11), 3.6-3.3 (m, 3H, C***H***$_2$N), 2.42 (brddd, J = 5.6, 11.4, 18.8 Hz, 1H, H-8), 2.25 (brdd, J = 5.8, 18.8 Hz, 1H, H-8′), 1.93 (brs, 3H, H-15), 1.78 (brdd, J = 5.6, 13.0 Hz, 1H, H-9β), 1.7-1.4 (m, 7H, H-9α, 2C***H***$_2$CH$_2$N, C***H***$_2$CH$_2$CH$_2$N), 1.34 (d, J = 6.7 Hz, 3H, H-13), 1.15 (s, 3H, H-14); ^{13}C NMR (50.3 MHz) δ 186.4 (C-3), 170.4 (C-12), 154.5 (C-1), 153.3, 146.3, 128.3 (C-4, C-5, C-7), 127.0 (C-2), 121.5 (C-6), 46.5, 43.0 (2***C***H$_2$N), 44.3 (C-11), 37.2 (C-10), 32.1 (C-9), 26.4 (C-8), 25.5, 24.3 (2***C***H$_2$CH$_2$N), 24.8 (C-14),23.6 (***C***H$_2$CH$_2$CH$_2$N), 17.0 (C-13), 9.9 (C-15).

4-[(11S)-3-Oxoeudesma-1,4,6-trien-12-oyl]-morpholine (**4c**): yield: 24% (recovered santonin 60%); yellow oil, $[\alpha]_D^{21}$ +193° (*c* 1.14); MS *m/e* 315 (M^+, 64), 300 (18), 201 (11), 115 (5), 114 (100); HRMS 315.1826, $C_{19}H_{25}NO_3$ required 315.1828; IR ν_{max} 1645, 1610, 835 cm^{-1}; ^1H NMR (200 MHz) δ 6.72 (d, J = 9.8 Hz, 1H, H-1), 6.47 (brs, 1H, H-6), 6.23 (d, J = 9.8 Hz, 1H, H-2), 3.8-3.4 (m, 8H, 2 C***H***$_2$O, 2C***H***$_2$N), 3.46 (q, J = 6.7 Hz, 1H, H-11), 2.43 (brddd, J = 5.8, 11.4, 18.3 Hz, 1H, H-8), 2.25 (ddd, J = 1.4, 6.3, 18.3 Hz, 1H, H-8′), 1.92 (brs, 3H, H-15), 1.79 (ddd, J = 1.4, 5.8, 13.1 Hz, 1H, H-9β), 1.56 (ddd, J = 6.3, 11.4, 13.1 Hz, 1H, H-9α), 1.35 (d, J = 6.7 Hz, 3H, H-13), 1.14 (s, 3H, H-14); ^{13}C NMR (50.3 MHz) δ 186.5 (C-3), 171.0 (C-12), 154.6 (C-1), 153.0, 145.8, 128.7 (C-4, C-5, C-7), 127.2 (C-2), 121.9 (C-6), 66.9, 66.6 (2***C***H$_2$O), 46.2, 42.4 (2***C***H$_2$N), 44.3 (C-11), 37.3 (C-10), 32.1 (C-9),25.0 (C-14). 23.8 (C-8), 17.0 (C-13), 10.1 (C-15).

1-[(11S)-3-Oxoeudesma-4,6-dien-12-oyl]-pyrrolidine (**5a**): yield: 78%; pale yellow solid, m.p. 90-92°C (hexane-EtOAc); $[\alpha]_D^{26}$ +471° (*c* 0.72); MS *m/e* 302 (M^++1, 35), 301 (M^+, 76), 286 (3), 204 (10), 98 (100);

HRMS 302.2116, $C_{19}H_{28}NO_2$ required 302.2113; IR ν_{max}, 1640, 1620, 850 cm^{-1}; ^1H NMR (200 MHz) δ 6.37 (brs, 1H, H-6), 3.6-3.4 (m, 4H, 2C***H***$_2$N), 3.35 (q, J = 6.9 Hz, 1H, H-11), 2.63 (ddd, J = 6.5, 13.3, 17.9 Hz, 1H, H-2), 2.42 (ddd, J = 2.9, 4.4, 17.9 Hz, 1H, H-2′), 2.4-2.2 (m, 2H, 2H-8), 2.0-1.6 (m, 7H, 2H-1, H-9β, 2C***H***$_2$CH$_2$N), 1.81 (s, 3H, H-15), 1.32 (d, J = 6.9 Hz, 3H, H-13), 1.09 (s, 3H, H-14);^{13}C NMR (50.3 MHz) δ 198.8 (C-3), 170.7 (C-12), 154.8, 148.5, 127.1 (C-4, C-5, C-7), 121.4 (C-6), 46.7 (C-11), 46.3, 45.9 (2 ***C***H$_2$N), 36.6, 36.0 (C-1, C-9), 33.6 (C-2), 32.8 (C-10), 23.5, 23.9, 26.0 (C-8, 2 ***C***H$_2$CH$_2$N), 21.0 (C-14), 16.3 (C-13), 10.1 (C-15).

1-[(11S)-3-Oxoeudesma-4,6-dien-12-oyl]-piperidine (**5b**): yield: 58%(recovered **2** 28%); yellow oil, $[\alpha]_D^{20}$ +406° (*c* 3.7); MS *m/e* 315 (M^+, 37), 203 (1), 175 (2), 113 (7), 112 (100), 84 (3); HRMS 315.2201, $C_{20}H_{29}NO_2$ required 315.2198; IR ν_{max} 1660-1620, 1600 cm^{-1} ; ^1H NMR (200 MHz) δ 6.35 (brd, J = 1.8 Hz, 1H, H-6), 3.5-3.3 (m, 4H, 2C***H***$_2$N), 3.46 (q, J = 6.8 Hz, 1H, H-11), 2.64 (ddd, J = 6.4, 13.4, 18.2 Hz, 1H, H-2), 2.43 (ddd, J = 2.8, 4.7, 18.2 Hz, 1H, H-2′), 2.4-2.2 (m, 2H, 2H-8), 1.80 (s, 3H, H-15), 1.32 (d, J = 6.8 Hz, 3H, H-13), 1.09 (s, 3H, H-14); ^{13}C NMR δ 198.9 (C-3), 170.4 (C-12), 154.7, 149.1, 127.2 (C-4, C-5, C-7), 121.3 (C-6), 44.9 (C-11), 46.5, 42,9 (2 ***C***H$_2$N), 36.7, 36.1 (C-1, C-9), 33.7 (C-2), 32.8 (C-10), 25.5, 26.3 (2 ***C***H$_2$CH$_2$N), 23.8, 24.3 (C-8, ***C***H$_2$CH$_2$CH$_2$N), 20.9 (C-14), 17.0 (C-13), 10.1 (C-15).

4-[(11S)-3-Oxoeudesma-4,6-dien-12-oyl]-morpholine (**5c**): yield: 34% (recovered **2** 50%); yellow oil, $[\alpha]_D^{20}$ +390° (*c* 2.4); MS *m/e* 317 (M^+, 74), 203 (13), 175 (8), 115 (7), 114 (100); HRMS 317.1993, $C_{19}H_{27}NO_3$ required 317.1991; IR ν_{max} 1670-1600, 1110 cm^{-1}; ^1H NMR (200 MHz) δ 6.34 (brd, J = 1.8 Hz, 1H, H-6), 3.41 (q, J = 6.9 Hz, 1H, H-11), 3.8-3.4 (m, 8H, 2C***H***$_2$N, 2C***H***$_2$O), 2.65 (ddd, J = 6.5, 13.2, 17.7 Hz, 1H, H-2), 2.43 (ddd, J = 2.9, 4.5, 17.7 Hz, 1H, H-2′), 2.3-2.2 (m, 2H, 2H-8), 1.79 (s, 3H, H-15), 1.32 (d, J = 6.9 Hz, 3H, H-13), 1.07 (s, 3H, H-14); ^{13}C NMR δ 198.6 (C-3), 170.8 (C-12), 154.2, 148.3, 127.3 (C-4, C-5, C-7), 121.5 (C-6), 66.6, 66.3 (2***C***H$_2$O). 45.8, 42.0 (2***C***H$_2$N), 44.3 (C-11), 36.5, 35.9 (C-1, C-9), 33.5 (C-2), 32.6 (C-10), 23.6 (C-8), 20.8 (C-14), 16.7 (C-13), 10.0 (C-15).

1-[(11S)-7αH-Eudesma-3,5-dien-12-oyl]-pyrrolidine (**6**): yield: 65% (recovered **3** 22%); yellow oil, $[\alpha]_D^{20}$ +17° (*c* 1.78); MS *m/e* 288 (M^++1, 55), 287 (M^+, 91), 286 (M^+-1, 16), 272 (39), 189 (25), 188 (67), 160 (100), 127 (63), 98 (43); HRMS 288.2323, $C_{19}H_{30}NO$ required 288.2320; IR ν_{max} 1629, 866 cm^{-1}; ^1H NMR (200 MHz) δ 5.49 (brs, 1H, H-3), 5.21 (brs, 1H, H-6), 3.6-3.4 (m, 4H, 2C***H***$_2$N), 2.6-2.4 (m, 1H, H-7), 2.38 (dq, J = 6.2, 8.8 Hz, 1H, H-11), 2.35-2.15 (m, 1H, H-2), 2.15-2.0 (m, 1H, H-2′), 2.0-1.8 (m, 6H, 2H-8, 2C***H***$_2$CH$_2$N), 1.68 (brs, 3H, H-15), 1.11 (d, J = 6.4 Hz, 3H, H-13), 0.94 (s, 3H, H-14); ^{13}C NMR δ 174.6 (C-12), 142.6, 130.8 (C-4, C-5), 124.6 (C-3), 122.3 (C-6), 46.6, 45.5 (2***C***H$_2$N), 44.0 (C-11), 39.6 (C-7), 37.8, 36.9 (C-1, C-9), 32.1 (C-10), 26.8, 24.3 (2***C***H$_2$CH$_2$N), 23.3 (C-14), 22.7 (C-2), 22.4 (C-8), 19.9 (C-15), 14.1 (C-13).

General procedure for the synthesis of compounds **7**.

To a 0°C cooled solution of unsaturated ketone amide **5** (0.23 mmol) and $CeCl_3.7H_2O$ (86 mg, 0.23 mmol) in MeOH (0.6 mL) it was added $NaBH_4$ (105 mg, 0.28 mmol). After 30 minutes at this temperature the reaction was quenched with aqueous NH_4Cl and the mixture extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography of the residue with hexane-EtOAc as eluent gave compound **7**.

1-[(11S)-3β-Hydroxyeudesma-4,6-dien-12-oyl]-pyrrolidine (**7a**): yield: 98%; yellow oil, $[\alpha]_D^{20}$ +298° (*c* 2.4); MS *m/e* 302 (M^+-1, 6), 301 (M^+-2, 28), 230 (4), 218 (7), 127 (10), 99 (6), 98 (100); HRMS 302.2071, $C_{19}H_{28}NO_2$ required 302.2120; IR ν_{max}, 3600-3100, 1630, 1610, 1010, 870 cm^{-1}; ^1H NMR (200 MHz) δ 6.12 (brs, 1H, H-6), 4.07 (brt, J = 7.2 Hz, 1H, H-3), 3.5-3.4 (m, 4H, 2C***H***$_2$N), 3.17 (q, J = 7.0 Hz, 1H, H-11), 1.74 (s, 3H, H-15), 1.24 (d, J = 7.0 Hz, 3H, H-13), 0.96 (s, 3H, H-14); ^{13}C NMR δ 171.6 (C-12), 138.9, 135.6, 129.2 (C-4, C-5, C-7), 121.1 (C-6), 71.5 (C-3), 46.6, 46.2 (2 ***C***H$_2$N), 45.9 (C-11), 37.4, 35.8 (C-1, C-9), 32.3 (C-10), 28.9 (C-2), 26.1 (***C***H$_2$CH$_2$N), 23.3, 24.1 (C-8, ***C***H$_2$CH$_2$N), 22.9 (C-14), 16.5 (C-13), 13.8 (C-15).

1-[(11S)-3β-Hydroxyeudesma-4,6-dien-12-oyl]-piperidine (**7b**): yield: 83%; yellow oil, $[\alpha]_D^{20}$ +239° (*c* 2.6); MS *m/e* 317 (M^+, 5), 316 (M^+-1, 7), 315 (M^+-2, 30), 300 (9), 299 (41), 284 (39), 188 (36), 187 (48), 112 (100); HRMS 317.2349, $C_{20}H_{31}NO_2$ required 317.2355; IR ν_{max} 3520-3200, 1640-1600, 1010 cm^{-1}; ^1H NMR (200 MHz) δ 6.12 (brs, 1H, H-6), 4.09 (brt, J = 8.0 Hz, H-3), 3.9-3.6 (m, 1H, C***H***$_2$N), 3.29 (q, J = 7.0 Hz, 1H, H-11), 3.5-3.2 (m, 3H, C***H***$_2$N), 1.75 (s, 3H, H-15), 1.25 (d, J = 7.0 Hz, 3H, H-13), 0.98 (s, 3H, H-14); ^{13}C NMR δ 171.5 (C-12), 139.6, 135.7, 129.2 (C-4, C-5, C-7), 120.9 (C-6), 71.7 (C-3), 46.5, 43.8 (2***C***H$_2$N), 44.5 (C-11), 37.6, 35.9 (C-1, C-9), 32.4 (C-10), 29.0 (C-2), 26.4, 24.6 (2***C***H$_2$CH$_2$N), 23.5, 22.8 (C-8, ***C***H$_2$CH$_2$CH$_2$N), 22.9 (C-14), 17.2 (C-13), 13.6 (C-15).

4-[(11S)-3β-Hydroxyeudesma-4,6-dien-12-oyl]-morpholine (**7c**): yield: 87%; yellow oil, $[\alpha]_D^{20}$ +238° (*c* 2.5); MS *m/e* 319 (M^+, 12), 318 (M^+-1, 12), 317 (M^+-2, 49), 302 (18), 301 (77), 188 (60), 187 (100), 177 (20), 171 (30), 143 (25), 114 (77); HRMS 319.2136, $C_{19}H_{29}NO_3$ required 319.2147; IR ν_{max} 3560-3140, 1660-1600, 1020 cm^{-1} ; ^1H NMR (200 MHz) δ 6.10 (brs, 1H, H-6), 4.06 (brt, J = 8.6 Hz, H-3), 3.3-3.7 (m, 8H, 2C***H***$_2$N, 2C***H***$_2$O), 3.23 (q, J = 6.7 Hz, H-11), 1.71 (s, 3H, H-15), 1.24 (d, J = 6.7 Hz, 3H, H-13), 0.94 (s, 3H, H-14); ^{13}C NMR δ 171.9 (C-12), 139.0, 135.4, 129.7 (C-4, C-5, C-7), 121.3 (C-6), 71.6 (C-3), 67.0, 66.6 (2***C***H$_2$O) 45.9, 42.2 (2***C***H$_2$N), 44.4 (C-11), 37.5, 35.8 (C-1, C-9), 29.0 (C-2), 32.4 (C-10), 23.5 (C-8), 22.9 (C-14), 17.1 (C-13), 13.8 (C-15).

General procedure for the synthesis of compounds **8**.

A solution of unsaturated ketone amide **5** (0.57 mmol) in dry THF (0.6 mL) was added dropwise to a suspension of $LiAlH_4$ (108 mg, 2.85 mmol) in dry THF (1.7 mL) at room temperature under argon. The reaction mixture was stirred for 30 minutes and quenched with aqueous NH_4Cl and then extracted with EtOAc. The organic layers were washed with brine and dried over Na_2SO_4. Flash chromatography eluting with hexane-EtOAc gave compound **8**.

1-[(11S)-3β-Hydroxyeudesma-4,6-dien-12-yl]-pyrrolidine (**8a**): yield: 91%; yellow oil, $[\alpha]_D^{20}$ +173° (*c* 2.9); MS *m/e* 289 (M^+, 1.3), 271(2), 188 (5), 173 (4), 85 (5), 84 (100); HRMS 289.2395, $C_{19}H_{31}NO$ required 289.2406; IR ν_{max} 3540-3170, 1640, 1115 cm^{-1}; ^1H NMR (200 MHz) δ 6.11 (brs, 1H, H-6), 4.10 (t, J = 4.8 Hz, 1H, H-3), 1.75 (s, 3H, H-15), 1.06 (d, J = 6.1 Hz, 3H, H-13), 0.99 (s, 3H, H-14); ^{13}C NMR δ 143.9, 136.2, 127.7 (C-4, C-5, C-7), 119.1 (C-6), 71.8 (C-3), 61.9 (C-12), 54.4 (2***C***H$_2$N), 41.0 (C-11), 37.7, 36.0 (C-1, C-9), 32.7 (C-10), 29.2 (C-2), 23.4, 23.3 (C-8, 2***C***H$_2$CH$_2$N), 22.9 (C-14), 18.1 (C-13), 13.8 (C-15).

1-[(11S)-3β-Hydroxyeudesma-4,6-dien-12-yl]-piperidine (**8b**): yield: 87%; yellow oil, $[\alpha]_D^{20}$ +178° (*c* 2.6); MS *m/e* 304 (M^++1, 47), 261 (42), 259 (13), 99 (10), 98 (100); HRMS 304.2637, $C_{20}H_{34}NO$ required 304.2640; IR ν_{max} 3510-3100, 1630, 1010 cm-1; ^1H NMR (200 MHz) δ 6.10 (brs, 1H, H-6), 4.09 (brt, J = 8.0 Hz, H-3), 1.77 (s, 3H, H-15), 1.06 (d, J = 6.8 Hz, 3H, H-13), 0.98 (s, 3H, H-14); ^{13}C NMR δ 143.8, 136.2, 127.8 (C-4, C-5, C-7), 119.2 (C-6), 71.7 (C-3), 64.3 (C-12), 54.7 (2***C***H$_2$N), 38.7 (C-11), 37.7, 36.6 (C-1, C-9), 32.7 (C-10), 29.2 (C-2), 25.6 (2***C***H$_2$CH$_2$N), 23.3, 22.9 (C-8, ***C***H$_2$CH$_2$CH$_2$N), 22.9 (C-14), 18.2 (C-13), 13.8 (C-15).

4-[(11S)-3β-Hydroxyeudesma-4,6-dien-12-yl]-morpholine (**8c**): yield: 85%; yellow oil, $[\alpha]_D^{20}$ +144° (*c* 3.08); MS *m/e* 305 (M^+, 0.5), 288 (1), 287 (5), 131 (3), 129 (2), 100 (100); HRMS 305.2360, $C_{19}H_{31}NO_2$ required 305.2355; IR ν_{max} 3520-3140, 1640, 1110, 1060, 860 cm^{-1}; ^1H NMR (200 MHz) δ 6.07 (brs, 1H, H-6), 4.09 (brt, J = 7.8 Hz, H-3), 3.67 (t, J = 4.8 Hz, 4H, 2C***H***$_2$O), 1.76 (s, 3H, H-15), 1.04 (d, J = 6.5 Hz, 3H, H-13), 0.98 (s, 3H, H-14); ^{13}C NMR δ 143.7, 136.2, 127.7 (C-4, C-5, C-7), 119.1 (C-6), 71.7 (C-3), 64.3 (C-12), 67.0 (2***C***H$_2$O), 53.9 (2***C***H$_2$N), 38.5 (C-11), 37.7, 35.9 (C-1, C-9), 29.1 (C-2), 32.7 (C-10), 23.7 (C-8), 22.8 (C-14), 17.8 (C-13), 13.8 (C-15).

General procedure for the synthesis of compounds **9**.

To a solution of compound **8** (0.2 mmol) in $CHCl_3$ (2 mL) at room temperature were added three portions of MnO_2 (1.8 mmol x 3) at intervals of 12 hours. After two days the reaction mixture was filtered through silica gel, concentrated *in vacuo* and chromatographed with hexane-EtOAc to give compound **9**.

1-[(11S)-3-Oxoeudesma-4,6-dien-12-yl]-pyrrolidine (**9a**): yield 73%; yellow oil, $[\alpha]_D^{22}$ +410° (*c* 2.2); MS *m/e* 287 (M^+, 10), 204 (2), 105 (2), 85 (12), 84 (100); HRMS 287.2239, $C_{19}H_{29}NO$ required 287.2242; IR ν_{max} 1635, 1610 cm-1; ^{1}H NMR (200 MHz) δ 6.30 (brs, 1H, H-6), 1.81 (s, 3H, H-15), 1.11 (d, J = 6.4 Hz, 3H, H-13), 1.07 (s, 3H, H-14); ^{13}C NMR δ 199.2 (C-3), 154.3, 155.9 (C-5, C-7), 126.3 (C-4), 120.0 (C-6), 61.6 (C-12), 54.3 (2 $\boldsymbol{C}H_2N$), 41.7 (C-11), 36.9, 36.3 (C-1, C-9), 33.8 (C-2), 33.2 (C-10), 23.6, 23.5 (C-8, 2 $\boldsymbol{C}H_2CH_2N$), 21.2 (C-14), 17.9 (C-13), 10.2 (C-15).

1-[(11S)-3-Oxoeudesma-4,6-dien-12-yl]-piperidine (**9b**): yield 79%; yellow oil, $[\alpha]_D^{22}$ +394° (*c* 2.2); MS *m/e* 302 (M^+, 2), 203 (1), 117 (2), 115 (2), 105 (2), 99 (15), 98 (100); HRMS 302.2482, $C_{20}H_{32}NO$ required 302.2484; IR ν_{max} 1650, 1615 cm^{-1}; ^{1}H NMR (200 MHz) δ 6.28 (d, J = 1.9 Hz, 1H, H-6), 1.81 (s, 3H, H-15), 1.53 (t, J = 5.4 Hz, 2C$\boldsymbol{H}_2CH_2N$), 1.08 (d, J = 6.7 Hz, 3H, H-13), 1.08 (s, 3H, H-14); ^{13}C NMR δ 158.9, 156.1, 126.1 (C-4, C-5, C-7), 119.6 (C-6), 199.2 (C-3), 64.6 (C-12), 54.9 (2 $\boldsymbol{C}H_2N$), 39.6 (C-11), 37.0, 36.3 (C-1, C-9), 33.2 (C-10), 33.8 C-2), 26.0 (2 $\boldsymbol{C}H_2CH_2N$), 24.3, 24.4 (C-8, $\boldsymbol{C}H_2CH_2CH_2N$), 21.0 (C-14), 17.7 (C-13), 10.1 (C-15).

4-[(11S)-3-Oxoeudesma-4,6-dien-12-yl]-morpholine (**9c**): yield 77%; yellow oil, $[\alpha]_D^{22}$ +370° (*c* 1.6); MS *m/e* 304 (M^+, 1), 203 (2), 131 (1), 105 (2), 101 (11), 100 (100); HRMS 304.2274, $C_{19}H_{30}NO_2$ required 304.2276; IR ν_{max} 1640, 1100 cm^{-1}; ; ^{1}H NMR (200 MHz) δ 6.27 (brd, J = 1.9 Hz, 1H, H-6), 3.65 (t, J = 4.5 Hz, 4H, 2C$\boldsymbol{H}_2O$), 1.80 (s, 3H, H-15), 1.09 (d, J = 5.2 Hz, 3H, H-13), 1.08 (s, 3H, H-14); ^{13}C NMR δ 199.1 (C-3), 155.7, 153.9, 126.4 (C-4, C-5, C-7), 120.0 (C-6), 64.0 (C-12), 67.0 (2 $\boldsymbol{C}H_2O$), 53.9 (2 $\boldsymbol{C}H_2N$), 39.2 (C-11), 37.0, 36.3 (C-1, C-9), 33.8 (C-2), 33.2 (C-10), 24.1 (C-8), 21.1 (C-14), 17.8 (C-13), 10.1 (C-15).

Preparation of 1-[(11S)-3,3-Ethanedithioeudesma-4,6-dien-12-oyl]-pyrrolidine (**10**).

A solution of **5a** (785 mg, 2.6 mmol), 99% ethanedithiol (6 mL, 71 mmol) and $BF_3.Et_2O$ (0.1 mL, 0.8 mmol) in HOAc (10 mL) was stirred at room temperature for 4 days and then concentrated to dryness by azeotropic distillation (benzene) *in vacuo*. The oily residue was chromatographed on silica gel eluting with hexane-EtOAc (9:1 to 1:1) to give 961 mg (98%) of compound **10** as a yellow oil, $[\alpha]_D^{22}$ +336° (*c* 3.4); MS *m/e* 377 (M^+, 98), 349 (15), 317 (50), 279 (34), 251 (19), 219 (18), 98 (100); HRMS 377.1848, $C_{21}H_{31}NOS_2$ required 377.1847; IR ν_{max} 1620, 1430 cm^{-1}; ^{1}H NMR (400 MHz) δ 6.11 (brs, 1H, H-6), 3.60-3.30 (m, 6H, 2 C$\boldsymbol{H}_2N$, C$\boldsymbol{H}_2S$), 3.25-3.15 (m, 2H, C$\boldsymbol{H}_2S$), 3.18 (q, J = 6.8 Hz, 1H, H-11), 2.43 (ddd, J = 2.8, 13.2, 14.4 Hz, 1H, H-2), 2.25 (td, J = 3.4, 14.4 Hz, 1H, H-2′), 2.19 (brdd, J = 6.0, 12.4 Hz, 1H, H-8), 2.07 (brd, J = 6.0, 1H, H-8′), 1.93 (brs, 3H, H-15), 1.95-1.86 (m, 2H, C$\boldsymbol{H}_2CH_2N$), 1.85-1.76 (m, 2H, C$\boldsymbol{H}_2CH_2N$), 1.61 (ddd, J = 2.8, 13.2, 13.6 Hz, 1H, H-1), 1.43-1.52 (m, 2H, H-1′, H-9β), 1.33 (ddd, J = 6.0, 12.4, 12.8, 1H, H-9α), 1.25 (d, J = 6.8, 3H, H-13), 0.94 (s, 3H, H-14); ^{13}C NMR δ 171.4 (C-12), 139.8, 137.5, 127.0 (C-4, C-5, C-7), 121.7 (C-6), 72.5 (C-3), 46.3 (C-11), 46.1, 45.8 (2$\boldsymbol{C}H_2N$), 41.4, 39.5 (2$\boldsymbol{C}H_2S$) 39.9 (C-2), 37.0, 36.9 (C-1, C-9), 31.9 (C-10), 26.0, 23.9 (2$\boldsymbol{C}H_2CH_2N$), 23.1 (C-8), 22.5 (C-14), 16.4 (C-13), 15.6 (C-15).

Preparation of (11S)-3,3-Ethanedithioeudesma-4,6-dien-12-ol (**11**).

To a 1M $LiAlH_4$ in THF solution (5 mL, 5 mmol) cooled at 0°C under Ar was added piperidine (1.5 mL, 15 mmol). The mixture was stirred at this temperature for 2 hours to obtain a 1M solution of lithium tripiperidinoaluminium hydride (LTPDA)[17] which was used as follows.

To a solution of compound **10** (92 mg, 0.24 mmol) in dry THF (0.24 mL) at 0°C under Ar, 1.92 mL (1.92 mmol) of the above solution was added in four portions (0.48 mL x 4) at intervals of 15 min and then two additional portions (1 mL x 2, 1 mmol x 2) and an aqueous solution of 4M $NaBH_4$ (1 mL, 4 mmol) at

intervals of 30 min. After stirring the mixture for additional 30 min the solution was extracted with EtOAc and the organic layers washed with brine and dried over Na_2SO_4 anh. Flash chromatography eluting with hexane-EtOAc (1:1) separated three compounds: 39 mg (53%) of **11**, 10 mg (11%) of starting material **10** and 19 mg (22%) of compound **12**.

Compound **11**: colorless oil, $[\alpha]_D^{22}$ +305° (*c* 1.7); MS *m/e* 310 (M^+, 70), 282 (34), 251 (17), 250 (100), 249 (24), 235 (13), 219 (25), 191 (11); HRMS 310.1426, $C_{17}H_{26}OS_2$) required 310.1425; IR ν_{max} 3640-3100, 1690, 1625, 1020 cm^{-1}; ^1H NMR (200 MHz) δ 6.13 (brs, 1H, H-6), 3.52 (brd, J = 7.5 Hz, 2H-12), 3.5-3.1 (m, 4H, 2C***H***$_2$S), 2.5-2.3 (m, 2H, H-2, H-11), 2.25 (dt, J = 3.4, 14.2 Hz, 1H, H-2′), 2.2-2.0 (m, 1H, H-8), 2.01 (brd, J = 5.1 Hz, 1H, H-8′), 1.95 (brs, 3H, H-15), 1.64 (td, J = 3.0, 13.1, 1H, H-1), 1.6-1.2 (m, 3H, H-1′, 2H-9), 1.03 (d, J = 6.9, 3H, H-13), 0.94 (s, 3H, H-14); ^{13}C NMR δ 141.6, 137.7, 126.8 (C-4, C-5, C-7), 121.9 (C-6), 72.5 (C-3), 65.6 (C-12), 44.0 (C-11), 41.6, 40.1, 39.7 (C-2, 2***C***H_2S), 37.3, 37.1 (C-1, C-9), 32.3 (C-10), 23.0 (C-8), 22.6 (C-14), 15.8, 15.3 (C-13, C-15).

Compound **12**: pale yellow oil; $[\alpha]_D^{22}$ +276° (*c* 1.95); MS *m/e* 363 (M^+, 1), 280 (4), 220 (3), 187 (1), 175 (3), 84 (100); HRMS 363.2045, $C_{21}H_{33}NS_2$ required 363.2054; IR ν_{max} 1610, 1415 cm^{-1}; ^1H NMR (200 MHz) δ 6.05 (brs, 1H, H-6), 3.5-3.0 (m, 4H, 2***C***H_2S), 1.93 (brs, 3H, H-15), 1.06 (d, J = 6.3 Hz, 1H, H-13), 0.94 (s, 3H, H-14); ^{13}C NMR δ 143.6, 137.9, 126.4 (C-4, C-5, C-7), 120.5 (C-6), 72.8 (C-3), 61.3 (C-12), 54.3 (2***C***H_2N), 41.5, 39.6 (2***C***H_2S), 40.3 (C-11), 40.1 (C-2), 37.3, 37.1 (C-1, C-9), 32.2 (C-10), 23.3 (2***C***$H_2$$CH_2$N), 23.1 (C-8), 22.6 (C-14), 18.2 (C-13), 15.7 (C-15).

Preparation of (11S)-3-Oxoeudesma-4,6-dien-12-ol (**13**).

To a solution of compound **11** (99 mg, 0.32 mmol) in 5 mL of CH_2Cl_2-MeOH (1:1) was added a solution of H_5IO_6 (140 mg, 0.59 mmol) in the minimum volume of water and the mixture was stirred at room temperature for 10 min. The reaction was quenched with an aqueous solution of $NaHSO_3$ and after the usual work up and chromatography with hexane-EtOAc (1:1) as eluent was isolated compound **13** (56 mg, 75%) which presents the following features: colorless oil, $[\alpha]_D^{22}$ +372° (*c* 1.96); MS *m/e* 234 (M^+, 78), 216 (6), 204 (36), 203 (100), 175 (68), 145 (10); HRMS 234.1620, $C_{15}H_{22}O_2$ required 234.1619; IR ν_{max} 3580-3180, 1640, 1610, 1015, 870 cm^{-1}; ^1H NMR (400 MHz) δ 6.35 (brd, J = 2.4 Hz, 1H, H-6), 3.62 (dd, J = 4.8, 10.3 Hz, 1H, H-12), 3.52 (dd, J = 4.0, 10.3 Hz, 1H, H-12′), 2.63 (ddd, J = 5.6, 14.4, 17.6 Hz, 1H, H-2), 2.54 (brsext., J = 6.8 Hz, 1H, H-11), 2.43 (ddd, J = 2.0, 4.8, 17.6 Hz, 1H, H-2′), 2.34 (brdddd, J = 2.4, 5.6, 12.8, 18.8 Hz, 1H, H-8), 2.15 (ddd, J = 1.6, 5.6, 18.8 Hz, 1H, H-8′), 1.80 (brs, 3H, H-15), 1.79 (dt, J = 4.8, 12.8, 14.4 Hz, 1H, H-1), 1.71 (ddd, J = 2.0, 5.6, 12.8 Hz, 1H, H-1′), 1.61 (ddd, J = 1.6, 5.6, 13.2 Hz, 1H, H-9), 1.52 (ddd, J = 5.6, 12.8, 13.2 Hz, 1H, H-9′), 1.10 (d, J = 6.8 Hz, 3H, H-13), 1.08 (s, 3H, H-14); ^{13}C NMR δ 199.3 (C-3), 155.4, 151.5, 126.7 (C-4, C-5, C-7), 121.2 (C-6), 65.8 (C-12), 44.4 (C-11), 36.8, 36.2 (C-1, C-9), 33.7 (C-2), 33.1 (C-10), 23.6 (C-8), 21.0 (C-14), 15.3 (C-13), 10.1 (C-15).

Preparation of (11S)-12-Phenylselenyl-3-oxoeudesma-4,6-diene (**14**).

To a solution of 55 mg of compound **13** (0.23 mmol) in 4.4 mL of dry CH_2Cl_2 under Ar were added successively *n*-Bu_3P (0.23 mL, 0.9 mmol) and a solution of *N*-phenylselenophtalimide (209 mg, 0.69 mmol) in dry CH_2Cl_2 (7.6 mL). After stirring at room temperature for 2 h, direct flash chromatography of the reaction mixture with hexane-EtOAc as eluent gave compound **14** (51 mg, 60%), a pale yellow oil: IR ν_{max} 3050, 1640, 1610, 1570, 1010, 870 cm^{-1}; ^1H NMR (200 MHz) δ 7.6-7.2 (m, 5H, Ar-H), 6.28 (brd, J = 2.2 Hz, 1H, H-6), 3.06 (dd, J = 7.8, 11.8 Hz, 1H, H-12), 2.96 (dd, J = 6.6, 11.8 Hz, 1H, H-12′), 2.7-2.5 (m, 2H, H-2, H-11), 2.42 (ddd, J = 2.7, 4.8, 17.5 Hz, 1H, H-2′), 1.80 (brs, 3H, H-15), 1.20 (d, J = 7.1 Hz, 3H, H-13), 1.07 (s, 3H, H-14); ^{13}C NMR δ 199.1 (C-3), 155.1, 152.1, 126.7 (C-4, C-5, C-7), 132.6, 128.9, 126.7, 120.7 (C-6, 5 aromatic C), 42.2 (C-11), 36.7, 36.2 (C-1, C-9), 33.7, 33.6 (C-2, C-12), 33.1 (C-10), 23.2 (C-8), 21.0 (C-14), 19.4 (C-13), 10.1 (C-15).

Preparation of (11S)-3-Oxoeudesma-4,6-diene (β-Cyperone) (**15**).

An ethanolic suspension of Raney nickel W-2 was added to a solution of compound **14** (15 mg, 0.04 mmol) in 1 mL of methanol, the resulting mixture stirred at room temperature for 15 min and then filtered on silica gel to give 8 mg (98%) of compound **15** with the following features: colorless oil, $[\alpha]_D^{20}$ +377° (*c* 1.5) [Lit.[18] $[\alpha]_D^{20}$ +232° (*c* 0.505, Cl_3CH)]; MS *m/e* 218 (M^+, 100), 203 (44), 190 (18), 175 (21), 147 (15), 119 (10); HRMS 218.1671, $C_{15}H_{22}O$ required 218.1670; IR ν_{max} 1640, 1610, 810 cm^{-1}; ^1H NMR (400 MHz) δ 6.27 (d, J = 2.4, 1H, H-6), 2.63 (ddd, J = 5.6, 14.4, 18.0 Hz, 1H, H-2), 2.48-2.38 (m, 2H, H-2′, H-11), 2.33 (brdddd, J = 2.4, 5.2, 12.8, 18.8 Hz, 1H, H-8), 2.16 (brddd, J = 1.6, 5.6, 18.8 Hz, 1H, H-8′), 1.83-1.75 (m, 1H, H-1), 1.81 (brs, 3H, H-15), 1.70 (ddd, J = 2.0, 5.6, 13.2 Hz, 1H, H-1′), 1.60 (ddd, J = 1.6, 5.2, 13.2 Hz, 1H, H-9), 1.50 (ddd, J = 5.6, 12.8, 13.2 Hz, 1H, H-9′), 1.09 (d, J = 5.6 Hz, 6H, H-13, H-12), 1.08 (s, 3H, H-14); ^{13}C NMR δ 199.2 (C-3), 156.2, 156.0, 126.3 (C-4, C-5, C-7), 118.2 (C-6), 37.1, 36.4 (C-1, C-9), 36.1 (C-11), 33.8 (C-2), 33.2 (C-10), 23.6 (C-8), 21.5, 21.1, 21.0 (C-12, C-13, C-14), 10.1 (C-15).

Preparation of (11S)-7αH-Eudesma-3,5-dien-12-ol (**16**).

To a solution of compound **6** (124 mg, 0.43 mmol) in dry THF (0.4 mL) at 0°C under Ar were added several portions of a 1M LTPDA solution, prepared as indicated above, at 20 min. intervals (2 x 0.8 mL, 4 x 1.6 mL). Forty minutes after the last addition, aqueous 4M $NaBH_4$ (1 mL) was added and the mixture extracted with EtOAc. Usual work up and chromatography with hexane-EtOAc gave compound **16** (22 mg, 23%), unreacted starting material **2** (58 mg, 47 %) and amine **17** (12 mg, 10%).

Compound **16**: colorless oil, $[\alpha]_D^{22}$ -104° (*c* 1.1); MS *m/e* 220 (M^+, 25), 101 (3), 190 (5), 189 (28), 187 (6), 162 (14), 161 (100), 105 (11); HRMS 220.1822, $C_{15}H_{14}O$ required 220.1827; IR ν_{max} 3640-3140, 3000, 1025, 1070, 860 cm^{-1}; ^1H NMR (400 MHz) δ 5.49 (brd, J = 4.8 Hz, 1H, H-3), 5.35 (brd, J = 2.4 Hz, 1H, H-6), 3.62 (dd, J = 6.4, 10.8 Hz, 1H, H-12), 3.54 (dd, J = 6.8, 10.8 Hz, 1H, H-12′), 2.47-2.40 (m, 1H, H-7), 2.30-2.18 (m, 1H, H-2), 2.03 (brdt, J = 5.6, 18.7 Hz, 1H, H-2′), 1.79 (brdq, J = 4.8, 6.8 Hz, 1H, H-11), 1.76 (brs, 3H, H-15), 1.62-1.52 (m, 2H, 2H-8), 1.52-1.46 (m, 1H, H-9), 1.46-1.32 (m, 3H, 2H-1, H-9′), 0.95 (s, 3H, H-14), 0.88 (d, J = 6.8 Hz, 3H, H-13); ^{13}C NMR δ 142.6, 131.3 (C-4, C-5), 124.2 (C-3), 123.6 (C-6), 66.2 (C-12), 40.2 (C-11), 38.3 (C-7), 38.0 (C-9), 37.2 (C-1), 32.3 (C-10), 23.3 (C-14), 22.8 (C-2), 20.1 (C-15), 19.7 (C-8), 12.7 (C-13).

Compound (**17**): yellow oil; MS *m/e* 273 (M^+, 54), 258 (5), 203 (13), 202 (75), 188 (10), 187 (48), 84 (100); HRMS 273.2457, $C_{19}H_{31}N$ required 273.2456; IR ν_{max} 1610 cm^{-1}; ^1H NMR δ 5.45 (brs, 1H, H-3), 5.31 (brd, J = 2.0 Hz, H-6), 2.6-2.4 (m, 6H, 3C***H***$_2$N), 1.74 brs, 3H, H-15), 0.93 (s, 3H, H-14), 0.84 (d, J = 7.0, 3H, H-13);; ^{13}C NMR δ 142.1, 131.3 (C-4, C-5), 124.8, 123.9 (C-3, C-6), 61.0 (C-12), 54.5 (2 ***C***H_2N), 39.6, 36.4 (C-7, C-11), 38.1, 37.2 (C-1, C-9), 32.3 (C-10), 23.4 (2***C***H_2CH$_2$N), 23.2 (C-14), 22.6 (C-2), 20.1 (C-15), 18.9 (C-8), 14.2 (C-13).

Preparation of (11S)-12-Methanesulphonyloxy-7αH-eudesma-3,5-diene (**18**).

A cooled solution (-15°C) of compound **16** (29 mg, 0.12 mmol) and Et_3N (36.5 μL, 0.26 mmol) in dry CH_2Cl_2 (0.9 mL) under argon was treated with 14 μL of MsCl (0.18 mmol) and the mixture stirred at this temperature for 20 min. The reaction mixture was transferred to a separatory funnel with the aid of more CH_2Cl_2 and was washed with iced water, 10% HCl, aqueous $NaHCO_3$. and brine, and dried over Na_2SO_4 anh. to give compound **18** (34.7 mg, 93%) as a colorless oil; ^1H NMR (200 MHz) δ 5.53 (brs, 1H, H-3), 5.28 (d, J = 2.5 Hz, 1H, H-6), 4.20 (dd, J = 7.0, 9.6 Hz, 1H, H-12), 4.10 (dd, J = 7.0, 9.6 Hz, 1H, H-12′), 3.00 (s, 3H, CH_3O-), 2.6-2.4 (m, 1H, H-7), 1.76 (s, 3H, H-15), 0.94 (d, J = 6.9 Hz, 3H, H-13), 0.96 (s, 3H, H-14); ^{13}C NMR δ 143.3, 131.0 (C-4, C-5), 124.8 (C-3), 122.0 (C-6), 72.8 (C-12), 38.1, 37.3 (C-7, C-11), 37.7, 37.1 (C-1, C-9), 37.3 (CH_3O), 32.3 (C-10), 23.3 (C-14), 22.8 (C-2), 20.1 (C-15), 19.6 (C-8), 12.7 (C-13)

Preparation of 7αH-Eudesma-3,5-diene (**19**).

To a solution of compound **18** (34.7 mg, 0.11 mmol) in dry THF (0.15 mL) at room temperature was added a 1M THF suspension of $LiBHEt_3$ (0.3 mL, 0.3 mmol) and the mixture stirred for 2h. After the addition of 0.1 mL of MeOH, the mixture was cooled at 0°C and treated with 0.2 mL of 33% H_2O_2. Extraction with pentane and usual work up gave 20 mg (82%) of compound **19** as a colorless oil with the following features: $[\alpha]_D^{20}$ -116° (*c* 2.4); MS *m/e* 204 (M^+, 44), 189 (13), 162 (21), 161 (100), 119 (8), 105 (10); HRMS 204.1885, $C_{15}H_{24}$ required 204.1878; IR ν_{max} 1471, 1450, 970, 862 cm^{-1}; ^1H NMR (400 MHz) δ 5.49 (brd, J = 5.2 Hz, 1H, H-3), 5.42 (brd, J = 2.0 Hz, 1H, H-6), 2.30-2.26 (m, 1H, H-2), 2.11 (brdt, J = 5.6, 10.8 Hz, 1H, H-7), 2.03 (brddd, J = 5.2, 5.6, 18.4 Hz, 1H, H-2'), 1.77 (brs, 3H, H-15), 1.66 (dsext., J = 2.0, 6.8 Hz, H-11), 1.62-1.53 (m, 1H, H-8), 1.38-1.32 (m, 1H, H-1), 0.94 (s, 3H, H-14), 0.91 and 0.88 (two d, J = 6.8 Hz, H-12, H-13); ^{13}C NMR δ 142.1, 131.5 (C-4, C-5), 124.0 (C-3), 123.9 (C-6), 43.0 (C-7), 38.3 (C-9), 37.4 (C-1), 32.5 (C-11), 29.7 (C-10), 23.4 (C-14), 23.0 (C-2), 21.0 (C-8), 20.2 (C-15), 19.7, 19.0 (C-13, C-14).

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