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Synthesis of two Natural 8-Oxo-β-cyperone Derivatives from (-)-Santonin.

Luz Cardona, Begoña García, Cristina L. García and José R. Pedro.*

Departament de Química Orgànica, Facultat de Química, Universitat de València, 46100-Burjassot (Valencia), Spain.

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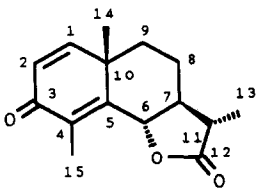
Abstract. This paper reports on the chemical transformations of (-)-santonin into (+)-8-oxo-β-cyperone and (+)-12-hydroxy-8-oxo-β-cyperone involving 8-oxo group introduction and elaboration of the side chain.

In earlier work, the authors used santonin **(1)** to prepare various natural sesquiterpene lactones, including both 6,12- and 8,12-olide moieties.[1,2] These natural products have aroused great interest on account of their wide spectrum of biological activities.This paper reports on the chemical transformation on (-)-santonin **(1)** into the natural 8-oxo-β-cyperone derivatives **2** and **3**, two eudesmane unsaturated diketones with antibiotic activity.[3] 8-Oxo-β-cyperone **(2)** was first isolated from *Isocoma wrightii*[4] and more recently from *Haplopappus freemontii*.[3] From this latter plant 12-hydroxy-8-oxo-β-cyperone **(3)** and its C_{11}-epimer were also isolated. A synthesis of the racemic form of **2** was previously reported.[5]



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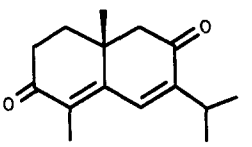

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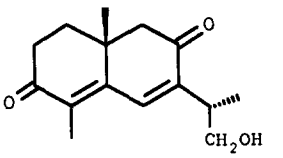

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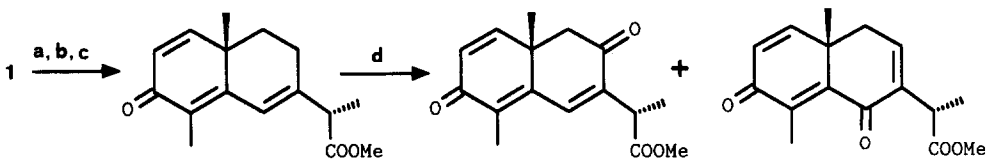
RESULTS AND DISCUSSION

The synthesis of compounds **2** and **3** from santonin **(1)** involved the introduction of 8-oxo group at the B ring, the hydrogenation of $\Delta^{1,2}$-double bond at the A ring and the reduction of the methyl ester to hydroxyl or methyl group at the side chain.

To reach the first target, the trienone **4** was prepared as we have recently described.[6] This preparation includes a methylation of the hydroxy-carboxylate of santonin with methyl iodide in *N,N*-dimethylformamide and *in situ* dehydration of the hydroxyl group at C-6 by treatment with thionyl chloride in pyridine. The

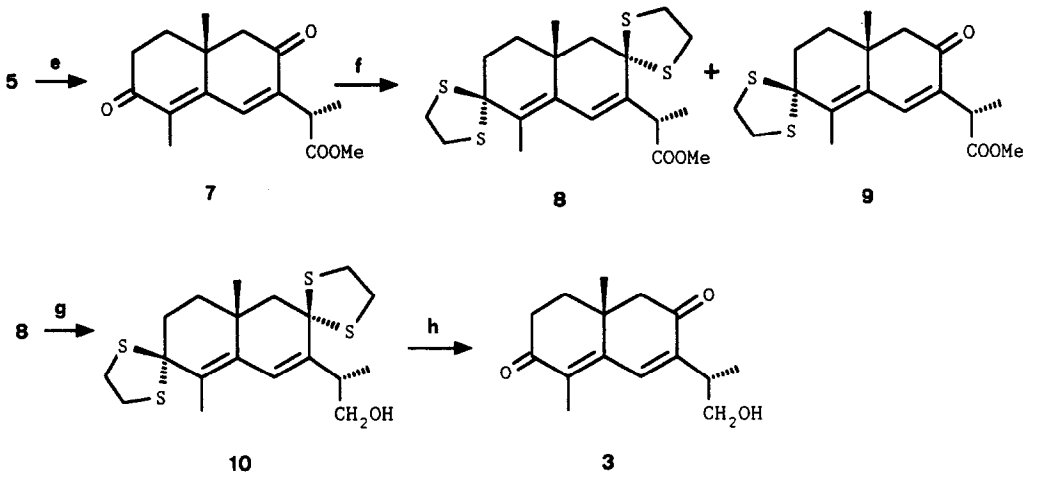
introduction of an oxo-group at C-8 on the trienone **4** had been previously reported[7] in variable yields (25-37%) by treatment with *tert*-butyl chromate-acetic anhydride in a carbon tetrachloride solution. In view of these results we thought to investigate the allylic oxidation of the trienone **4** with several iminium chlorochromate type reagents, such as pyridinium (PCC)[8] , quinolinium[9] and 4-(dimethylamino)pyridinium[10] chlorochromate. Acceptable results were obtained with pyridinium chlorochromate and although the yield of **5** (26-40%) was similar to the previously reported,[7] in our case the unreacted starting trienone **4** could be recovered (43-22%) and efficiently recycled.



Reagents: (a) NaOH; (b) MeI; (c) $SOCl_2$, pyr; (d) pyridinium chlorochromate

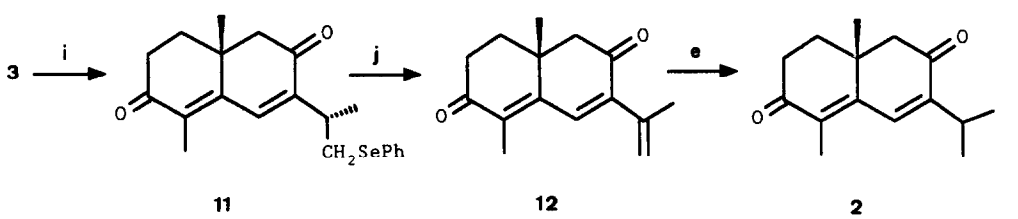
Once the 8-oxo group was introduced, compound **5** was hydrogenated catalytically with tris(triphenylphosphine)-chlororhodium (Wilkinson catalyst) in benzene for 24 h to give 95% yield of 1,2-dihydroderivative **7**.

In order to elaborate the side chain of compound **7** a protection of the 3- and 8-oxo groups is required. The dioxolan group[11,12] is the most commonly used protective group for ketones. However it is know that the preparation of dioxolans from unsaturated ketones is accompanied by shift of the double bond and that the resulting dioxolans are extremely sensitive to acidic conditions. The use of thioketals circumvents both disadvantages. So, by reaction of dicarbonyl compound **7** with ethanedithiol in acetic acid-boron trifluoride[13] for 9 days with azeotropic removal of water in the last steps and column chromatography on neutral alumina, we obtained compound **8** in 81% yield. Shorter reaction times or no strictly controlled reaction conditions resulted in a lower yield in compound **8** and in a higher yield of 3-monothioketal **9.** The reduction of 3,8-dithioketal **8** with lithium aluminum hydride in THF gave the corresponding alcohol **10** in 83% yield. Initial experiments of thioketal cleavage with *N*-bromosuccinimide (NBS/CH_3CN)[14] and cerium ammonium hexanitrate (CAN/CH_3CN)[15] were unsuccessfull as they gave rise to complex mixture of products. With $Tl(NO_3)_3$/MeOH[16] for 5 min we could isolate diketone **3** in 46% yield and finally satisfactory results were obtained with periodic acid[17] in CH_2Cl_2-MeOH-H_2O at room temperature for 20 min yielding **3** (71%). From the point of view of the practical preparation of the diketone **3**, the three steps of oxo-group protection, reduction with lithium aluminum hydride and thioketal cleavage can be carried out without purification of the intermediate products in an overall yield of 49%.



Reagents: (e) H_2, Wilkinson catalyst; (f) $(CH_2SH)_2$, BF_3; (g) $LiAlH_4$/THF; (h) periodic acid

The obtainment of the isopropyl unit present in **2** was first tackled starting from **10** by conversion of the hydroxyl group into an other group that could subsequently be reduced into a hydrocarbon (MsO-, TsO-). However treatment of compound **10** with mesyl chloride/pyridine a complex reaction mixture was obtained, due probably to mesylation at the sulphur atoms.[18] Nevertheless, starting from **3** we carried out the substitution of the hydroxyl group by a phenylselenyl group by treatment with *N*-phenylselenophtalimide/tri-*n*-butylphosphine (NPSP-Bu_3P),[19] obtaining compound **11** in a 72% yield. Reductive removal of the phenylseleno group was first tried with triphenyltin hydride[20] and with nickel boride.[21] The first reagent gave rise to unreacted starting material, whilts the latter allowed us to isolate compound **2** with low yield (24%) due to concomitant reduction of double bonds. Finally, removal of the phenylseleno group was carried out in indirect way by oxidation of the selenide to selenoxide and spontaneous elimination to give compound **12** (87% yield) and subsequent hydrogenation over Wilkinson catalyst, which yielded compound **2** in a 63% yield.



Reagents: (i) NPSP-Bu_3P; (j) H_2O_2; (e) H_2, Wilkinson catalyst

The ^1H and ^{13}C NMR spectra of the synthetic products are fully consistent with structures **2** and **3** and identical with literature data[3,4] of the natural products isolated from *Isocoma wrightii* and *Haplopappus freemontii* respectively.

Table 1. ^{13}C NMR Data of Compounds (2)-(3), (6)-(12) (50.3 MHz, $CDCl_3$, δ values)

C	(2)	(3)	(6)	(7)*	(8)[A]	(9)*[A]	(10)*[A]	(11)[B]	(12)
1	35.7	35.7	153.5	35.5	36.5	36.7	36.5	35.6	35.6
2	33.5	33.6	126.6	33.3	39.3[a]	39.0	39.4	33.8[a]	33.5
3	198.3[a]	198.2[a]	186.4[a]	198.0[a]	72.0	71.4	72.1	198.3[b]	198.1[a]
4	133.1[b]	133.9[b]	136.6[b]	134.4[b]	136.4[b]	135.9[a]	136.4[a]	133.8[c]	134.2[b]
5	151.9[b]	151.2[b]	149.7[b]	150.8[b]	130.4[b]	136.8[a]	129.2[a]	151.4[c]	151.7[b]
6	133.3	135.9	190.0[a]	136.3	126.2	138.5	123.6	135.8	135.2
7	148.6[b]	144.3[b]	140.5[b]	140.7[b]	140.0[b]	139.1[a]	144.0[a]	144.8[c]	141.4
8	197.6[a]	198.8[a]	141.4	196.4[a]	68.3	197.0	68.3	197.5[b]	197.6
9	52.8	52.5	38.5	51.7	57.6	52.2	57.6	52.6	53.8
10	37.3	37.3	42.3	37.1	34.7	36.3	34.5	37.1	37.5
11	27.0	35.5	39.1	38.7	42.0	38.1	38.8	34.8	139.2
12	21.6[c]	67.3	174.1	173.8	176.0	174.6	69.1	33.5[a]	120.0
13	21.8[c]	15.6	15.7	15.9	19.8	16.1	20.2	19.8	22.1
14	23.6	23.7	23.6	23.4	24.1	24.5	24.5	23.6	23.5
15	10.9	11.1	11.9	10.9	15.8	16.5	15.8	11.1	11.1
CH_3O-	-	-	52.0	52.0	52.0	51.9	-	-	-

*Assignment by heteronuclear ^1H-^{13}C correlation (HMQC)

[A] CH_2S carbons for compound **(8)**, 39.8[a],40.4[a],40.7[a], 41.7[a]; for compound **(9)**, 39.9, 41.9; for compound **(10)**, 39.8, 40.3, 41.5, 41,7.

[B] Aromatic signals for compound **(11)**:123.6,126.9,129.0,132.7,134.3

[a,b,c] Chemical shifts are interchangeables.

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 Bruker AC-200 instrument (200.1 MHz for ^1H NMR and 50.3 MHz for ^{13}C) or a Varian Unity 400 (399.95 MHz for ^1H and 100.58 MHz for ^{13}C) by using $CDCl_3$ solutions. The carbon type (methyl, methylene, methine, or quaternary) was determined by DEPT experiments. Mass spectra were recorded at 70 ev. Optical rotations were determined on a Polartronic D (Schmidt and Haensch) polarimeter as solution in $CHCl_3$. Flash chromatography was carried out using SDS Chromagel 60 Kieselgel except otherwise stated, when Scharlau neutral Alumina Al835 was used.

Methyl (11S)-3,8-dioxoeudesm-1,4,6-trien-12-oate (**5**).

To a stirred slurry of PCC (3.60 g, 16.70 mmol) and anhydrous NaOAc (0.051 g, 0.62 mmol) in dry CH_2Cl_2 (10 mL) under argon was added a solution of compound **4** (0.545 g, 2.09 mmol) in CH_2Cl_2 (10 mL). After heating under reflux for 7.5 days, the overlaying solution was decanted and the solid residue washed with ether. The combined organic layers were filtered through silica gel with ether as eluent and concentrated *in vacuo* to give an orange oil. Chromatography with hexane-EtOAc mixtures (8:2 to 5:5) separated three compounds: unreacted starting product **4** (221 mg, 41%), 8-oxoderivative **5** (169 mg, 29%) and 6-oxoderivative **6** (64 mg, 11%).

Compound **5**: pale yellow crystals, m.p. 123-125°C (hexane-CH_2Cl_2); $[\alpha]_D^{22}$ +261° (c 5.7); MS *m/e* 274 (M^+, 61), 259 (M^+-CH_3, 28), 242 (M^+-CH_3OH, 55), 215 (M^+-$COOCH_3$, 77), 214 (100), 200 (35), 199 (44); IR ν_{max} 2980-2890, 1737, 1675, 1645, 1620, 1210 cm^{-1}; ^1H NMR δ 7.46 (br.s, 1H, H-6), 6.79 (d, 1H, J= 9.9 Hz, H-1), 6,32 (d, 1H, J= 9.9 Hz, H-2), 3.76 (br.q, 1H, J= 7,3 Hz, H-11), 3.67 (s, 3H, -OCH_3), 2.62 (d, 1H, J= 16.0 Hz, H-9), 2.44 (d, 1H, J= 16.0 Hz, H-9'), 2,08 (br.s, 3H, H-15), 1.42 (d, 3H, J= 7.3 Hz, H-13), 1.34 (s, 3H, H-14).

Compound **6**: yellow crystals, m.p. 100-102°C (hexane-CH_2Cl_2); $[\alpha]_D^{22}$ -223° (c 0.56); MS *m/e* 275 (M^++1, 3), 274 (M^+, 17), 259 (M^+-CH_3, 11), 242 (M^+-CH_3OH, 17), 215 (M^+-$COOCH_3$, 22), 199 (100); IR ν_{max} 2980-2890, 1725, 1650, 1630, 1225, 1160 cm^{-1}; ^1H NMR δ 6.80 (d,1H, J= 10.0 Hz, H-1), 6.75 (dt, 1H, J= 0.9 and 4.0 Hz, H-8), 6.31 (d, 1H, J= 10.0 Hz, H-2), 3.66 (br.q, 1H, J= 7.2 Hz, H-11), 3.66 (s, 3H, -OCH_3), 2.60 (d, 1H, J= 18.0 Hz, H-9), 2.53 (br.d, 1H, J= 18.0 Hz, H-9') 2.04 (br.s, 3H, H-15), 1.36 (d, 3H, J= 7.2 Hz, H-13), 1.32 (s, 3H, H-14).

Methyl (11S)-3,8-dioxoeudesma-4,6-dien-12-oate (**7**).

Compound **5** (337 mg, 1.23 mmol) in benzene (8.5 mL) was added (via syringe) to a prerreduced solution of $(Ph_3P)_3RhCl$ (200 mg) in a mixture of benzene-EtOH (30 mL, 29:1). This mixture was stirred overnight under H_2 at atmospheric pressure, the solvent was removed *in vacuo* and the oily residue purified by flash chromatography (hexane-EtOAc 6:4) to yield 320 mg (95%) of compound **7** as a yellow oil with the following features: $[\alpha]_D^{23}$ +361° (c 0.88); MS *m/e* 277 (M^++1, 2), 276 (M^+, 11), 244 (M^+-CH_3OH, 18), 217 (M^+-$COOCH_3$, 25), 216 (66), 200 (10); IR ν_{max} 3010-2890, 1730, 1670, 1170, 1200 cm^{-1}; ^1H NMR δ 7.28 (br.s, 1H, H-6), 3.71 (br.q, 1H, J= 7.3 Hz, H-11), 3.65 (s, 3H, -OCH_3), 2,70-2.50 (m, 2H, H-2), 2.51 (br.d, 1H, J= 16.0 Hz, H-9), 2.43 (d, 1H, J= 16.0 Hz, H-9'), 2.00 (td, 1H, J= 6.5 and 13.0 Hz, H-1α), 1.94 (br.s, H, 3H-15), 1.82 (ddd, 1H, J= 2.8, 4.9 and 13.0 Hz, H-1ß), 1.38 (d, 3H, J= 7.3 Hz, H-13), 1.27 (s, 3H, H-14).

Methyl (11S)-3,3,8,8-diethanedithioeudesma-4,6-dien-12-oate (**8**)

To a solution of compound **7** (89 mg, 0.32 mmol) in HOAc (2.3 mL) were added 1 mL of ethanedithiol (11.92 mmol) and two drops of $BF_3{\cdot}Et_2O$. The reaction mixture was stirred at room temperature for 9 days and then concentrated to dryness by azeotropic distillation at reduced pressure with dry benzene (3 x 50 mL). The green oil residue was purified by flash chromatography on neutral alumina (hexane: EtOAc mixtures 10:0 to 80:20) eluted 111 mg (81%) of dithioketal **8** and 7 mg (6%) of monothioketal **9**.

Compound **8**: yellow oil, $[\alpha]_D^{23}$ +214° (c 0.96); MS *m/e* 430 (M^++2, 21), 429 (M^++1, 24), 428 (M^+, 100), 413 (M^+-CH_3, 10), 369 (M^+-$COOCH_3$, 7), 335 (M^+-$C_2H_5S_2$, 21), 321 (59), 313 (23) 309 (17), 281

(16), 275 (18), 261 (22); IR ν_{max} 2990-2840, 1730, 1665, 1200, 1165 cm^{-1}; ^1H NMR δ 6.37 (br.s, 1H, H-6), 3.64 (s, 3H, $-OCH_3$), 3.61 (br.q, 1H, J= 7.2 Hz, H-11), 3.50-3.10 (m, 8H, $2SCH_2CH_2S$), 2.40 (td, 1H, J= 3.0 and 14.1 Hz, H-2β), 2.38 (br.d, 1H, J= 14.1 Hz, H-9), 2.22 (dt, 1H, J= 3,6 and 14.1 Hz, H-2α), 2.17 (d, 1H, J= 14.1 Hz, H-9'), 1.95 (br.s, 3H, H-15), 1.70-1.50 (m, 2H, H-1), 1.46 (d, 3H, J= 7.2 Hz, H-13), 1.14 (s, 3H, H-14).

Compound **9**: yellow oil, $[\alpha]_D^{23}$ +413° (c 4.6); MS *m/e* 352 (M^+, 3), 293 (M^+-$COOCH_3$, 2), 292 (4), 264 (2), 261 (2), 199 (2), 59 (100); IR ν_{max} 2990-2860, 1730, 1660, 1600, 1190, 1150 cm^{-1}; ^1H NMR δ 7.14 (br.s, 1H, H-6), 3.66 (br.q, 1H, J= 7.3 Hz, H-11), 3.63 (s, 3H, $-OCH_3$), 3.60-3.20 (m, 4H, $-SCH_2CH_2S-$), 2.50-2.20 (m, 2H, H-2) 2.34 (br.s., 2H, H-9), 2.10 (br.s., 3H, H-15), 1.83 (td, 1H, J= 3.7 and 12.5 Hz, H-1α), 1.60 (dt, 1H, J= 3.3 and 13.5 Hz, H-1β), 1.32 (d, 3H, J= 7.3 Hz, H-13), 1.11 (s, 3H, II-14).

(11S)-3,3,8,8-Diethanedithioeudesma-4,6-dien-12-ol (**10**)

Compound **8** (104 mg, 0.24 mmol) in dry THF (19 mL) was added dropwise to a 0°C cooled suspension of $LiAlH_4$ (52 mg, 1.36 mmol) in THF (1.8 mL). After stirring at this temperature for 20 min. the reaction was quenched with aqueous saturated NH_4Cl and extracted with ether. The combined organic layers were washed with aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography of the residue with hexane-EtOAc (8:2) as eluent yielded 79 mg (83%) of compound **10** as a pale yellow oil with the following features: $[\alpha]_D^{20}$ +235° (c 1.99); MS *m/e* 402 (M^++2, 21), 401 (M^++1, 27), 400 (M^+, 100), 385 (M^+-CH_3, 16), 341 (10), 313 (22), 308 (M^+-$C_2H_4S_2$, 12), 307 (36), 281 (38), 247 (35) 245 (22), 215 (34); IR ν_{max} 3600-3200, 2980-2860, 1030, 1010 cm^{-1}; ^1H NMR δ 6.23 (br.s, 1H, H-6), 3.63 (br.dd, 1H, J= 7.5 and 10.5 Hz, H-12), 3.55 (br.dd, 1H, J=6.6 and 10.5 Hz, H-12'), 3.50-3.20 (m, 8H, $2-SCH_2CH_2S-$), 2.72 (quint., 1H, J= 7.0 Hz, H-11), 2.42 (br.d, 1H, J= 14.0 Hz, H-9), 2.40 (br.td, 1H, J= 4.4 and 12.5 Hz, H-2ß), 2.25 (d, 1H, J= 14.0 Hz, H-9'), 2.23 (dt, 1H, J= 3.0 and 12.5 Hz, H-2α), 1.94 (s, 3H, H-15), 1.73 (td, 1H, J= 3.0 and 13.0 Hz, H-1α), 1.51 (dt, 1H, J=4.0 and 13.0 Hz, H-1ß), 1.22 (d, 3H, J= 7.0 Hz, H-13), 1.14 (s, 3H, H-14).

(11S)-3,8-dioxoeudesma-4,6-dien-12-ol or (+)-12-hydroxy-8-oxo-β-cyperone (**3**) *from compound* **10**.

a) Reaction with $Tl(NO_3)_3$: To a solution of compound **10** (15 mg, 0.037 mmol) in MeOH (1 mL) was added $Tl(NO_3)_3 \cdot 3H_2O$ (73 mg, 0.165 mmol). After stirring 5 min at room temperature the mixture was poured on water and extracted with EtOAc as usual. Column chromatography with hexane-EtOAc mixtures (8:2 to 4:6) afforded 4.2 mg (46%) of compound **3** as an oil with the following features: $[\alpha]_D^{21}$ +388° (c 0.13); MS *m/e* 249 (M^+-1, 0.7), 248 (M^+, 3), 247 (M^+-1, 1), 231 (M^+-OH, 12), 230 (M^+-H_2O, 63), 219 (M^+-CHO, 21), 218 (M^+-CH_2O, 100), 217 (M^+-CH_2OH, 10), 210 (25); IR ν_{max} 3650-3150, 2980-2880, 1680-1610, 1020 cm^{-1}; ^1H NMR δ (7.24 (br.s, 1H, H-6), 3.68 (dd, 1H, J= 5.6 and 10.3 Hz, H-12), 3.61 (dd, 1H, J= 6.6 and 10.3 Hz, H-12'), 3.08 (br. sext., J= 6.6 Hz, H-11), 2.59 (dd, 1H, J= 5.1 and 13.0 Hz, H-2ß), 2.57 (dd, 1H, J= 2.8 and 6.5 Hz, H-2α), 2.53 (d, 1H, J= 15.0 Hz, H-9), 2.44 (d, 1H, J= 15.0 Hz, H-9'), 2.00 (dt, 1H, J= 6.5 and 13.0 Hz H-1α), 1.97 (s, 3H, H-15), 1.82 (ddd, 1H, J= 2.8, 5.0 and 13.0 Hz, H-1ß), 1.26 (s, 3H, H-14), 1.17 (d, 3H, J = 7.2 Hz, H-13).

b) Reaction with H_5IO_6: A solution of 29 mg (0.127 mmol) of H_5IO_6 in the minimum volume of water was added to a solution of compound **10** (29 mg, 0.072 mmol) in 1.2 mL of CH_2Cl_2-MeOH (1:1) mixture. The dark brown solution was stirred at room temperature for 20 min. and then quenched with an aqueous solution

of $NaHSO_3$. By the usual workup and chromatography as before was obtained compound **3** (13 mg, 71%).

(11S)-3,8-dioxoeudesma-4,6-dien-12-ol or (+)-12-hydroxy-8-oxo-β-cyperone (**3**) *from compound* **7**.

To a solution of compound **7** (288 mg, 1.04 mmol) in HOAc (7.3 mL) were added ethanedithiol (3 mL, 35.76 mmol) and $BF_3 \cdot Et_2O$ (7 drops). The reaction mixture was stirred at room temperature for 5 days and then concentrated to dryness by azeotropic distillation at reduced pressure with dry benzene (3 x 50 mL).

The green oily residue was dissolved under argon with dry THF (13 mL), the solution cooled to 0°C, and then 206 mg (5.428 mmol) of $LiAlH_4$ were quickly added. After stirring at 0°C for 20 min the reaction was quenched with aqueous saturated NH_4Cl added in small portions and extracted as usual.

The oily residue was dissolved in 9.2 mL CH_2Cl_2-MeOH (1:1) mixture and then a freshly prepared solution of H_5IO_6 (302 mg, 1.32 mmol) in the minimun volume of water was added. The reaction mixture was stirred at room temperature for 15 min and then quenched with an aqueous solution of $NaHSO_3$. The usual workup and chromatography gave 127 mg (49%) of compound **3**.

(11S)-12-Phenylselenoeudesma-4,6-dien-3,8-dione (**11**).

To a solution of 26 mg (0.104 mmol) of compound **11** in dry CH_2Cl_2 (2 mL) under argon were added successively *n*-Bu_3P (0.105 mL, 0.420 mmol) and a solution of *N*-phenylselenophtalimide (95 mg, 0.314 mmol) in dry CH_2Cl_2 (3.4 mL). After stirring at room temperature for 1h the reaction mixture was diluted with ether and then concentrated to dryness. Flash chromatography with hexane-EtOAc mixtures (9:1 to 8:2) provided compound **11** (29 mg, 72%) as a pale yellow oil with the following features: IR ν_{max} 2980-2920, 1680-1620 cm^{-1}; ^1H NMR δ 7.50-7.40 (m, 2H, Ar-H *orto* to Se), 7.30-7.20 (m, 3H, Ar-H *meta* and *para* to Se), 7.13 (br.s, 1H, H-6), 3.21 (dd, 1H, J= 6.4 and 10.8 Hz, H-12), 3.02 (dd, 1H, J= 5.7 and 10.8 Hz, H-12'), 3.20-3.05 (m, 1H, H-11), 2.59 (dd, 1H, J= 5.1 and 12.5 Hz, H-2ß), 2.57 (dd, 1H, J = 2.6 and 7.1 Hz, H-2α), 2.38 (br. s, 2H, H-9), 1.97 (td, 1H, J= 7.1 and 13.0 Hz, H-1α), 1.93 (br.s, 3H, H-15), 1.79 (ddd, 1H, J= 2.6, 5.1 and 13.0 Hz, H-1ß), 1.26 (d, 3H, J= 6.4 Hz, H-13), 1.22 (s, 3H, H-14).

Eudesma-4,6-dien-3,8-dione or (+)-8-oxo-β-cyperone (**2**).

a) Reduction with Nickel Boride: To a solution of 26 mg (0.067 mmol) of compound **11** and 35 mg (0.147 mmol) of $NiCl_2 \cdot 6H_2O$ in 0.7 mL of THF-MeOH (2.7:1) cooled at 0°C were added 10 mg (0.263 mmol) of $NaBH_4$. The dark resulting mixture was stirred at 0°C for 15 min and then filtered through Celite with THF (10 mL) and EtOAc. The combined organic solutions were washed with aqueous saturated NH_4Cl and worked up as usual. After chromatography with hexane-EtOAc (9:1) as eluent was isolated compound **14** (4 mg, 25%) as a colourless viscous oil with the following features: $[\alpha]_D^{20}$ +390° (c 0,6); IR ν_{max} 3000-2860, 1680-1640 cm^{-1}; ^1H NMR δ 7.16 (br.s, 1H, H-6), 3.02 (br.sept., 1H, J= 6.7 Hz, H-11), 2.58 (dd, 1H, J= 4.8 and 14.0 Hz, H-2ß), 2.56 (dd, 1H, J= 2.4 and 5.6 Hz, H-2α), 2.50 (br.d, 1H, J= 15.6 Hz, H-9), 2.41 (d, 1H, J= 15.6 Hz, H-9'), 2.02 (dt, 1H, J= 5.6 and 14.0 Hz, H-1α), 1.95 (s, 3H, H-15), 1.80 (ddd, 1H, J= 2.4, 4.8 and 14.0 Hz, H-1ß), 1.24 (s, 3H, H-14), 1.13 (d, J= 7.2 Hz, H-12), 1.10 (d, 3H, J= 6.8 Hz, H-13).

b) Through Eudesma-4,6,11(12)-trien-3,8-dione (**12**): To a stirred solution of compound **11** (28 mg, 0.072 mmol) in THF (2 mL) cooled at 0°C were added 34 μL (0.141 mmol) of 30% H_2O_2. After 10 min at this temperature a second portion of 30% H_2O_2 (25 μL, 0.104 mmol) was added and the solution further stirred for 30 min. The reaction was warmed to room temperature for 1h and then diluted with brine. Workup followed by

flash chromatography eluting with hexane-EtOAc (8:2) gave compound **12** (14.5 mg, 87%) as a very unstable colourless oil which must be reduced without delay.

Compound **12**: ^{1}H NMR δ 7.29 (s, 1H, H-6), 5.52 (br.s,1H, H-12), 5.28 (br.s, 1H, H-12'), 2.75-2.50 (m, 2H, 2H-2), 2.61 (br.d, 1H, J= 14.6 Hz, H-9), 2.41 (d, 1H, J= 14.6 Hz, H-9'), 2.20-2.00 (m, 1H, H-1α), 1.99 (br.s, 3H, H-13), 1.97 (s, 3H, H-15), 1.81 (ddd, 1H, J= 2.6, 5.2 and 13.4 Hz, H-1ß), 1.26 (s, 3H, H-14).

To a prerreduced solution of $(Ph_3P)_3RhCl$ (14 mg, 0.035 mmol) in dry benzene (0.7 mL) was added (via syringe) a solution of compound **12** (8 mg, 0.035 mmol) in benzene-MeOH (4.2 mL, 20:1). After stirring overnight under H_2 at atmospheric pressure, the solvent was removed *in vacuo* and the residue chromatographed with hexane-EtOAc (7:3) as eluent to give 5 mg (62%) of (+)-8-oxo-ß-cyperone **2**.

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