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Synthesis of (+)-Isoalantolactone and (+)-Isoalloalantolactone from (-)-Santonin

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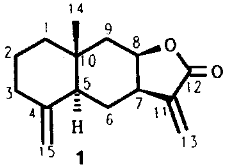
Abstract. This paper reports on the chemical conversion of (-)-santonin into (+)-isoalantolactone and (+)-isoalloalantolactone involving functionality transfer from C_6 to C_8, refunctionalization of the ring A and the formation of the α-methylene-8 β,12-olide moiety.

Isoalantolactone (1) and isoalloalantolactone (2) are two members of the eudesmane class of sesquiterpenes with an α-methylene-γ-lactone moiety.[1] These compounds have considerable biological activities as allergenic[2] and cytotoxic[3] agents, inhibitors of plant germination[4], antifungal,[5] nematocidal[6] and feeding deterrent activity against pest insects.[7]

Isoalantalactone (1) is a metabolite very characteristic of *Inula* species,[1] of which several synthesis of racemic form are reported.[8] On the other hand, isoalloalantolactone (2) was first found by Kalsi *et al.* from *Inula racemosa*[9] and afterwards by Bohlmann *et al.* from *Artemisia iwayomogi.*[10] Isoallolalantolactone (2) was obtained as a secondary product in a synthesis of 1-deoxyivangustin from artemisin.[11]

As part of our current synthetic program related to natural sesquiterpene lactones with biological activity, we now report the successful transformation of santonin (3) into the two above mentioned lactones (1) and (2).



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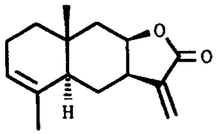

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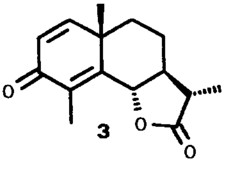

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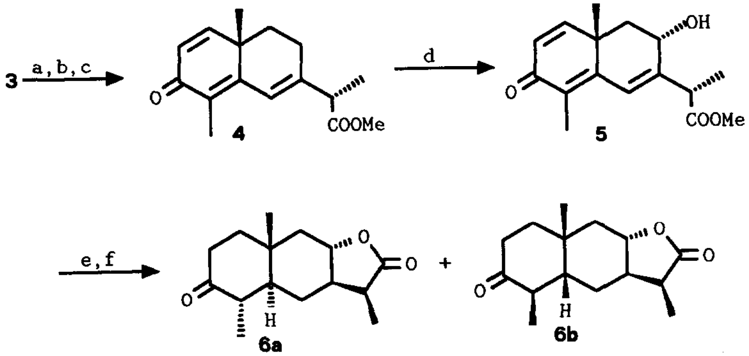
RESULTS AND DISCUSSION

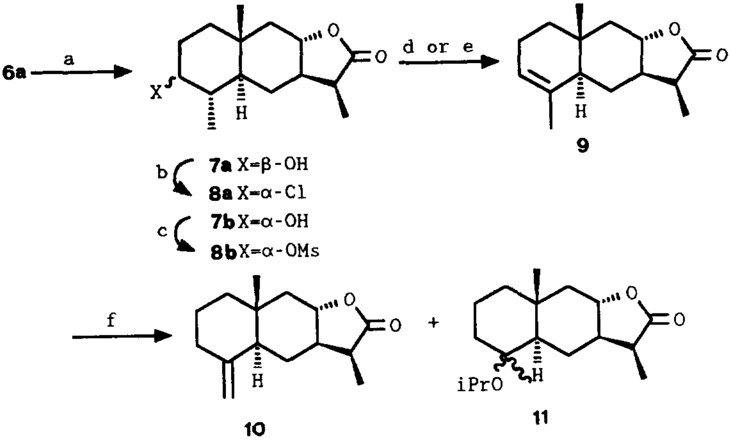
For the purpose of the synthesis of 8,12-lactonized eudesmanolides 1 and 2, introduction of an oxygen function at the C_8 position of santonin is necessary. Recently[12] we have reported a functionality transfer from C_6 to C_8 in santonin, which includes the preparation of the trienone 4 and subsequent allylic oxidation to give 5. Once the oxygen function was transferred from C_6 to C_8, the product 5 was hydrogenated catalytically with carbon-supported palladium in acetone. Heating the crude hydrogenated mixture with benzene and *p*-toluenesulfonic acid yielded lactones **6a** and **6b**.



Reagents: (a) NaOH; (b) MeI; (c) $SOCl_2$, pyr; (d) SeO_2; (e) H_2, Pd/C; (f) *p*-TsOH.

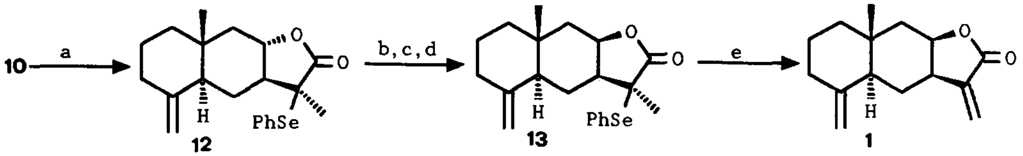
With the *trans*-fused isomer **6a** in our hands the synthesis of compounds **1** and **2** involves the refunctionalization of the ring A and the formation of the α-methylene-8β,12-olide moiety.

To reach the first target, the *trans*-fused isomer **6a** was converted into the epimeric alcohols **7a** and **7b** (4.6:1, 74% yield) with $NaBH_4$ in EtOH, which were dehydrated of indirect fashion. Conversion of the alcohol **7a** into its 3α-chloro derivative **8a** with $SOCl_2$-pyridine[13] at 80-85°C (64% yield) or with $POCl_3$-pyridine[14] at room temperature (81% yield), followed by elimination of the chloride with LiBr-Li_2CO_3/DMF[15] yielded **9** exclusively (92% yield). Alkene **9** can also be obtained, though with a lower selectivity ($\Delta^{2,3}/\Delta^{3,4}$ = 1:9) from **7b** by formation of mesylate **8b** (95% yield) and subsequent elimination with Li_2CO_3[15] (76% yield). In this way, the overall yield of conversion of product **6** into alkene **9** is 54%. The isomerization of the double bond C_3-C_4 to exocyclic position C_4-C_{15} was carried out by irradiation[16] of a solution of **9** in *i*-PrOH/xylene with a high-pressure 125 w mercury lamp, which yielded the expected product **10** (60% yield) along with the corresponding isopropyl ether **11** (9% yield).



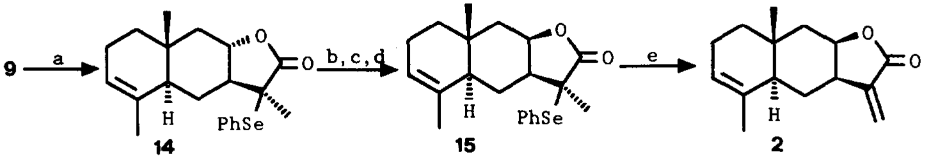
Reagents: (a) $NaBH_4$; (b) $POCl_3$, pyr; (c) MsCl, pyr; (d) LiBr, Li_2CO_3; (e) Li_2CO_3; (f) hν.

Once alkenes **9** and **10** were obtained, we applied our attention to reach the second target, *i.e.* the formation of the α-methylene-8β,12-olide moiety. To reach this second target, which involves the inversion of the configuration at C_8 and the introduction of the *exo*-methylene via the corresponding phenylselenoderivatives (PhSeCl/LDA),[17] the order of the events is crucial to obtain a good yield. Because of the convex shape of the molecule with the 8β,12-olide moiety, the phenylselenyl chloride tends to attack the lactone enolate from the less hindered α-face and consequently the subsequent *syn*-elimination should give rise mainly to the endocyclic C_7-C_{11} double-bond isomer.[11,18] On the contrary in molecules with an 8α,12-olide moiety, the penylselenyl chloride attacks the lactone enolate from the β-face and consequently the elimination should give rise the exocyclic C_{11}-C_{13} double-bond isomer.[18] Consistent with this reasoning, we have carried out, first the phenylselenylation ot the 8α,12-lactone **10**, which furnished the corresponding derivative **12** (65% yield) and afterwards the inversion of the configuration at C_8 by Lansbury method,[19] involving the saponification of the lactone and sequential treatment of the isolated dry sodium salt with mesyl chloride in THF and aqueous NaOH at 50°. In this way, the 11β-phenylselenyl-8β,12-lactone **13** was obtained with 32% yield along with a 24% yield of recovered starting product **12**. Finally, by oxidation of **13** with hydrogen peroxide and elimination, isoalantolactone (**1**) was obtained (80% yield) and was found to be identical with the natural material (melting point, optical rotation and ^{1}H NMR spectrum) [1,8].



Reagents: (a) LDA, PhSeCl; (b) NaOH; (c) CH_3SO_2Cl, Et_3N; (d) NaOH; (e) 30% H_2O_2

In the similar way, the 8α,12-lactone **9** was transformed into isoalloalantolactone (**2**). Its ^{1}H and ^{13}C NMR spectra are entirely consistent with the structure **2** and identical with literature data[9,10] of (+)-isoalloalantolactone (melting point, optical rotation and ^{1}H NMR spectrum).



Reagents: (a) LDA, PhSeCl; (b) NaOH; (c) CH_3SO_2Cl, Et_3N; (d) NaOH; (e) 30% H_2O_2.

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 ^{1}H NMR and 50.3 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 Perkin-Elmer polarimeter as solution in $CHCl_3$.

Table 1. ^{13}C NMR Data of Compounds (7)-(11) (50.3 MHz, $CDCl_3$, δ values).

C	(7a)	(7b)	(8a)	(9)	(10)	(11)[A]
1	44.5	44.7	44.7	43.3	44.1	47.9[a]
2	29.9	28.4	30.0	22.6[a]	22.5	19.3[b]
3	75.6	71.1	67.9	121.3	36.4	40.7[a]
4	38.4	34.9	34.9	133.4	149.0	86.9
5	49.2[a]	48.5[a]	48.6[a]	47.4	50.6	54.0[c]
6	23.1	23.0	23.0	23.0[a]	23.3	20.2[b]
7	48.2[a]	43.2[a]	43.5[a]	40.1[b]	48.1	48.9[c]
8	78.0	78.2	78.0	78.4	78.8	78.3
9	38.8	34.8	34.9	37.7	41.9	38.5
10	35.6	36.1	36.2	35.0	38.2	36.7
11	38.7	38.8	38.9	39.0[b]	38.9	39.1
12	180.2	180.2	180.0	180.2	180.0	180.5
13	9.2	9.6	9.5	9.3	9.6	9.6
14	15.0[b]	16.0[b]	17.7[b]	16.9[c]	17.9	19.1[d]
15	18.1[b]	17.2[b]	18.1[b]	21.2[c]	106.4	20.7[d]

[A] Isopropyl group: 25.2, 25.3 and 61.8.

[a,b,c,d] Chemical shifts are interchangeable.

3β-Hydroxy- and 3α-hydroxy-5,7,11αH,4,8βH-eudesman-8,12-olide **(7a)** *and* **(7b)**.

To a solution containing 1.474 g (4.69 mmol) of compound **(6a)**[12] in 80 mL of anhydrous EtOH cooled at 0°C, 1.243 g (32.80 mmol) of $NaBH_4$ was added in portions. The resulting mixture was stirred at 0°C for 45 min, after which aqueous saturated NH_4Cl was added. The mixture was extracted with EtOAc and the combined organic layers washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography with hexane-EtOAc mixtures eluted 0.166 g (13%) of compound **7b**: mp 146-148°C (hexane-EtOAC); $[\alpha]_D^{25}$ -115° (c 1.14, $CHCl_3$); MS *m/e* 252 (0.7, M^+), 235 (1.0), 219 (14.0), 208 (15.3), 193 (35.3), 190 (100), 175 (75.6), 161 (51.2), 147 (74.8); HRMS 252.1715, $C_{15}H_{24}O_3$ requires 252.1719; IR ν_{max} 3550, 3000-2900, 1770, 1220, 1000 cm^{-1}; ^{1}H NMR δ 0.92 (*s*, 3H, H-14), 0.93 (*d*, J = 5.2 Hz, 3H, H-15), 1.15 (*d*, J = 7.5 Hz, 3H, H-13), 1.39 (*t*, J = 11.6 Hz, 1H, H-9α), 1.81 (*dt*, J = 3.5 and 15.1 Hz, 1H, H-2β), 1.96 (*dd*, J = 4.0 and 11.6 Hz, 1H, H-9β), 2.1-1.9 (*m*, 1H, H-7), 2.62 (*quint*, J = 7.5 Hz, 1H, H-11), 3.78 (*br.s.*,1H, H-3) and 4.24 (*dt*, J = 4.0 and 11.6 Hz, 1H, H-8); ^{13}C NMR (Table 1).

A second product eluted was compound **7a** (0.756 g, 60%) with the following features: mp 129-131°C (hexane-EtOAc); $[\alpha]_D^{25}$ -69° (c 0.54, $CHCl_3$); MS *m/e* 252 (0.4, M^+), 237 (0.2), 235 (1.0), 219 (5.7), 208 (10.9), 190 (29.8), 175 (43.1), 161 (46.0), 147 (51.4), 121 (91.7), 107 (100), 93 (91.6); HRMS 252.1714, $C_{15}H_{24}O_3$ requires 252.1719; IR ν_{max} 3450-3100, 2980-2860, 1780,1200, 1010, 1000 cm^{-1}; ^{1}H NMR δ 0.95 (*s*, 3H, H-14), 0.97 (*d*, J = 6.5 Hz, 3H, H-15), 1.15 (*d*, J = 7.8 Hz, 3H, H-13), 1.29 (*t*, J = 11.6 Hz, 1H, H-9α), 2.00 (*dd*, J = 3.9 and 11.6 Hz, 1H, H-9β), 2.62 (*quint*, J = 7.5 Hz, 1H, H-11), 3.12 (*dt*, J = 5.2 and 10.2 Hz, 1H, H-3) and 4.24 (*dt*, J = 3.9 and 11.5 Hz, 1H, H-8); ^{13}C NMR (Table 1).

Table 2. ^{13}C NMR Data of compounds (1)-(2) and (12)-(15) (50.3 MHz, CDCl$_3$, δ values)

C	(12)^A	(13)^A	(14)^A	(15)^A	(1)	(2)
1	43.8	41.9	43.1	41.3	41.4	40.9
2	22.5	22.7	22.6^a	22.2^a	22.7	22.2
3	36.3	36.7	121.5	122.2	36.8	122.3
4	148.7	148.9	133.2	133.1	148.9	133.0
5	50.6	47.0^a	47.4	48.8	46.2	43.9^a
6	24.0	25.6	23.6^a	24.8^a	27.5	27.4
7	56.8	47.6^a	57.6	44.5	40.6	41.2^a
8	77.1	76.5	77.3	77.6	76.8	77.0
9	41.5	42.1	37.6	37.8	42.2	37.8
10	38.3	34.5	35.1	31.0	34.3	30.9
11	49.3	54.5	49.3	53.9	142.2	142.0
12	176.6	178.8	176.6	178.9	170.5	170.6
13	22.5	23.3	22.5	23.7	119.9	120.2
14	17.8	17.8	16.9^b	17.3^b	17.6	17.2^b
15	106.7	106.9	21.3^b	21.2^b	106.6	21.1^b

^{A} Aromatic carbons for compound (12) and (14): 124.3, 129.0, 129.5 and 138.1; for compound (13) and (15): 128.9, 137.8 and 138.1.
^{a,b,c} Chemical shifts are interchangeable.

3α-Chloro-5,7,11αH,4,8βH-eudesman-8,12-olide (**8a**).

To a solution of 0.190 g (0.764 mmol) of compound **7a** in dry pyridine (1 mL) was added a solution of POCl$_3$ (0.3 mL, 3.21 mmol) in dry pyridine (2 mL). After stirring 24 h at room temperature, the reaction was quenched by adding aqueous saturated NH$_4$Cl. The mixture was extracted with EtOAc, washed with 1N HCl and brine, dried (Na$_2$SO$_4$), and concentrated *in vacuo*. The reaction product was chromatographed on silica gel with 4:1 hexane-EtOAc mixture yielding 0.165 g (81%) of compound **8a**, with the following features: mp 126-128°C (hexane-EtOAc); $[\alpha]_D^{25}$ -120° (c 0.55, CHCl$_3$); MS *m/e* 228 and 226 (5.9 and 17.8, M$^+$-CO$_2$), 213 and 211 (9.2 and 27.6), 199 and 197 (7.1 and 22.4), 185 and 183 (32.2 and 92.6), 107 (100); IR ν_{max} 2980-2860, 1775, 1200, 1000 cm^{-1}; ^{1}H NMR δ 0.94 (*s*, 3H, H-14), 0.96 (*d*, J = 6.4 Hz, 3H, H-15), 1.15 (*d*, J = 7.7 Hz, 3H, H-13), 1.44 (*t*, J = 11.6 Hz, 1H, H-9α), 1.98 (*dd*, J = 3.9 and 11.6 Hz, 1H, H- 9β), 2.63 (*quint, J = 7.7, 1H, H-11), 4.24 (dt*, J = 3.9 and 11.6 Hz,1H, H-8) and 4.31 (*br.s.* overlapped with H-8, 1H, H-3) ; ^{13}C NMR (Table 1).

3α-(O-Methanesulfonyl)-5,7,11αH,4,8βH-eudesman-8,12-olide (**8b**).

To a solution of 44 mg (0.175 mmol) of compound **7b** in 4 mL of dry pyridine a 0°C was added 130 μL (1.68 mmol) of mesyl chloride. After stirring at 0°C for 24 h, the mixture was diluted with EtOAC and the reaction quenched with 9 mL of 2% HCl. By the usual work-up and chromatography with 7:3 hexane-EtOAc mixture as eluent was obtained 64 mg (95%) of compound **8b**, with the following features: an oil; ^{1}H NMR δ 0.95 (*s*, 3H, H-14), 0.99 (*d*, J = 6.6 Hz, 3H, H-15), 1.16 (*d*, J = 7.5 Hz, 3H, H-13), 2.01 (*dd*, J = 4.0 and 11.6 Hz, 1H, H-9β), 2.64 (*quint*, J = 7.5 Hz, 1H, H-11), 3.00 (*s*, 3H, CH$_3$-SO$_2$-), 4.24 (*dt*, J = 4.0 and 11.6 Hz, 1H, H-8) and 4.81 (*br.d*, J = 2.4 Hz, 1H, H-3).

5,7,11αH,8βH-eudesm-3-en-8,12-olide (**9**).

From compound (**8a**). A suspension of compound **8a** (0.176 g, 0.65 mmol), LiBr (0.149 g, 1.72 mmol) and Li_2CO_3 (0.173 g, 2.34 mmol) in dry DMF (2.4 mL) was heated at 140°C for 2.25 h. The reaction was quenched with aqueous saturated NH_4Cl and the mixture extracted with EtOAc. By the usual work-up and chromatography with 17:3 hexane-EtOAc mixture as eluent 142 mg (92%) of compound **9** was obtained. Compound **9** had the following features: mp 80-82°C (hexane-ether) $[\alpha]_D^{25}$ -92° (c 1.03, $CHCl_3$); MS *m/e* 234 (24.4, M^+), 219 (100), 191 (17.4), 175 (16.5), 161 (20.8), 149 (48.3), 121 (10.8),107 (63.6), 84 (76.9); HRMS 234.1623, $C_{15}H_{22}O_2$ requires 234.1614; IR ν_{max} 3010, 2980-2880, 1775, 995, 830 cm^{-1}; ^1H NMR δ 0.88 (*s*, 3H, H-14), 1.17 (*d*, J = 7.5 Hz, 3H, H-13), 1.36 (*t*, J = 11.5 Hz, 1H, H-9α), 1.61 (*br.s.*, 3H, H-15), 2.02 (*dd*, J = 4.1 and 11.5 Hz, 1H, H-9β), 2.2-1.9 (*m*, 4H, overlapped signals, 2 H-2, H-5, H-7), 2.65 (*quint*, J = 7.5 Hz, 1H, H-11), 4.34 (*dt*, J = 4.1 and 11.5 Hz, 1H, H-8) and 5.32 (*br.s.*, 1H, H-3); ^{13}C NMR (Table 1).

From compound (**8b**). A suspension of **8b** (51 mg, 0.15 mmol) and Li_2CO_3 (97 mg, 1.31 mmol) in dry DMF (4 mL) was heated at 140°C for 3 h, after which was diluted with EtOAc, washed with saturated aqueous NH_4Cl and brine. Chromatography as above give 27 mg (76%) of compound **9**.

5,7,11αH,8βH-eudesm-4(15)-en-8,12-olide (**10**).

A solution of 70 mg (0.299 mmol) of compound **9** and xylene (0.15 mL) in 14 mL of degasified *i*-PrOH was irradiated with a 125 W high pressure Hanovia lamp at room temperature over 4 h. After *in vacuo* removal of solvent the mixture was chromatographed with 9:1 hexane-EtOAc mixture as eluent yielding compound **10** (42 mg, 60%) and the isopropylether derivative **11** (8 mg, 9%). Compound **10** had the following features: an oil; $[\alpha]_D^{25}$ -33° (c 1.89, $CHCl_3$); MS *m/e* 234 (4.7, M^+), 219 (6.8), 191 (2.1), 175 (3.5), 147 (7.7), 121 (5.2), 91 (38.0), 41 (100); HRMS 234.1621, $C_{15}H_{22}O_2$ requires 234.1614; IR ν_{max} 2990-2880, 1780, 1650, 990, 890 cm^{-1}; ^1H NMR δ 0.80 (*s*, 3H, H-14), 1,17 (*d*, J = 7.8 Hz, 3H, H-13), 1.40 (*t*, J = 11.5 Hz, 1H, H-9α), 1.8-1.3 (*m*, 4H, 2 H-1, H-2, H-6), 2.04 (*dd*, J = 4.1 and 11.6 Hz, 1H, H-9β), 2.2-1.8 (*m*, 3H, H-7, H-6, H-5), 2.31 (*ddd*, J = 1.2, 3.1 and 11.8 Hz, 1H, H-3β), 2.62 (*quint*, J = 7.6 Hz, 1H, H-11), 4.22 (*dt*, J = 4.0 and 11.5 Hz, 1H, H-8), 4.45 (*d*, J = 1.3 Hz, 1H, H-15) and 4.73 (*d*, J = 1.3 Hz, 1H, H-15'); ^{13}C NMR (Table 1).

Compound **11** had the following features: mp 104-106°C (hexane-dichloromethane); $[\alpha]_D^{25}$ -75° (c 0.67, $CHCl_3$); MS *m/e* 294 (1.0, M^+), 279 (0.4), 251 (1.2), 235 (6.7), 234 (9.5), 209 (22.4), 206 (31.4), 190 42.3), 121 (100); HRMS 294.2195, $C_{18}H_{30}O_3$ requires 294.2187; IR ν_{max} 2960-2850, 1770, 1145, 1100, 1040, 980 cm^{-1}; ^1H NMR δ 0.97 (*s*, 3H, H-14), 1.04 (*d*, J = 6.1 Hz, 3H, CH_3-CH), 1.05 (*d*, J = 6.1 Hz, 3H, CH_3-CH), 1.05 (*s*, 3H, H-15), 1.17 (*d*, J = 7.6 Hz, 3H, H-13), 1.38 (*t*, J = 11.5 Hz, H-9α), 1.93 (*dd*, J = 3.8 and 11.5 Hz, 1H, H-9β), 2.05 (*m*, overlapped with H-9β, 1H, H-7), 2.63 (*quint.*, J = 7.6 Hz, 1H, H-11), 3.80 (*sept.*, J = 6.1 Hz, 1H, Me_2CH-O), and 4.19 (*dt*, J = 3.8 and 11.5 Hz, 1H, H-8); ^{13}C NMR (Table 1).

11β-Phenylseleno-5,7αH,8βH-eudesm-4(15)-en-8,12-olide (**12**).

To a THF solution of lithium diisopropylamide prepared from 0.093 mL (0.66 mmol) of diisopropylamine, 1.6 M *n*-BuLi in hexane (0.40 mL, 0.64 mmol) and 1 mL of dry THF at -78°C was added dropwise 75 mg (0.321 mmol) of compound **10** in 1 mL of dry THF. After stirring at -78°C for 1 h, 0.130 g (0.661 mmol) of phenylselenyl chloride in 2 mL of THF and 0.1 mL of HMPA was added dropwise at -78°C. The mixture was stirred at the same temperature for 1 h, then warmed to -35°C and kept at this temperature for 45 min. The reaction was quenched by adding 5 mL of 0.5 M HCl and the mixture extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*, yielding an oil which was chromatographed on silica gel; an 19:1 hexane-EtOAc mixture eluted from the column 81 mg (65%) of compound **12**, with the following features: mp 111-113°C (hexane-dichloromethane); IR ν_{max} 3060, 2980-2840, 1770, 1645, 1440, 1380, 1000, 890, 745, 690 cm^{-1}; ^{1}H NMR δ 0.84 (*s*, 3H, H-14), 1.41 (*t*, J = 11.0 Hz, 1H, H-9α), 1.53 (*s*, 3H, H-13), 2.07 (*dd*, J = 4.3 and 11.0 Hz, 1H, H-9β), 2.34 (*ddd*, J = 1.2, 3.1 and 11.8 Hz, 1H, H-3β), 4.50 (*dt*, J = 4.3 and 11.0 Hz, 1H, H-8), 4.54 (*d*, J = 1.0 Hz, 1H, H-15), 4.79 (*d*, J = 1.2 Hz, 1H, H-15'), 7.4-7.2 (*m*, 3H, aromatic) and 7.63 (*dd*, J = 1.4 and 7.3 Hz, 2H, aromatic); ^{13}C NMR (Table 2).

11β-Phenylseleno-5,7,8αH-eudesm-4(15)-en-8,12-olide (**13**).

A solution of 56 mg (0.144 mmol) of compound **12** in 8.8 mL of 96% aqueous ethanol was treated with 0.5 mL of 1M aqueous NaOH and the mixture was refluxed for 45 min, after which the solvent was removed *in vacuo* and residual water was eliminated by repeated azeotroping with benzene. The residual salt thus obtained was suspended in 7.5 mL of THF, cooled at 0°C and treated with 0.38 mL (2.74 mmol) of triethylamine, followed by 0.18 mL (2.37 mmol) of mesyl chloride. After 3 h, 3.8 mL of a 0.25 M NaOH solution was added and the mixture was warmed at 50°C for 3 h. After acidification with 15 mL of 5% HCl, the usual procedure and column chromatography with 19:1 hexane-EtOAc yielded 14 mg (24%) of starting product **12** and 19 mg (32%) of its epimer **13**, with the following features: mp 160-162°C (hexane-ether); IR ν_{max} 3070, 3050, 2980-2820, 1750, 1700, 1660, 1640, 1210, 1165, 1085, 970, 880, 740, 690 cm^{-1}; ^{1}H NMR δ 0.83 (*s*, 3H, H-14), 1.45 (*dd*, J = 4.4 and 15.6 Hz, 1H, H-9α), 1.57 (*s*, 3H, H-13), 2.21 (*dd*, J = 2.0 and 15.6 Hz, 1H, H-9β), 2.29 (*ddd*, J = 2.0, 5.0 and 12.0 Hz, 1H, H-7), 2.35 (*ddd*, J = 1.2, 3.1 and 11.8 Hz, 1H, H-3β), 4.55 (*d*, J = 1.3 Hz, 1H, H-15), 4.73 (*dt*, J = 2.0 and 4.4 Hz, 1H, H-8), 4.80 (*d*, J = 1.2 Hz, 1H, H-15), 7.4-7.2 (*m*, 3H, aromatic) and 7.79 (*dd*, J = 2.0 and 7.6 Hz, 2H, aromatic); ^{13}C NMR (Table 2).

5,7,8αH-Eudesma-4(15),11(13)-dien-8,12-olide or isoalantolactone (**1**).

To a solution containing 13 mg (0.033 mmol) of compound **13** in 0.4 mL of THF cooled to 0°C was added 10 μL (0.088 mmol) of 30% H_2O_2. The mixture was stirred at room temperature for 1 h and then poured into brine. The usual procedure yielded 6.2 mg (80%) of isoalantolactone **1**, with the following features: mp 112-113°C (diluted ethanol); $[\alpha]_D^{25}$ +168° (c 0.28, $CHCl_3$); MS *m/e* 232 (55.4, M^+), 217 (35.7), 191 (19.6), 190 (100), 176 (30.4), 164 (30.4), 117 (67.9); HRMS 232.1464, $C_{15}H_{20}O_2$ requires 232.1458; IR ν_{max} 2980-2820, 1750, 1660, 1635, 1260, 1135, 960, 885, 810; ^{1}H NMR δ 0.81 (*s*, 3H, H-14), 1.49 (*dd*, J = 5.1 and 15.6 Hz, 1H, H-9α), 1.72 (*ddd*, J = 2.5, 7.0 and 15.7 Hz, 1H, H-6α), 2.18 (*dd*, J = 1.2 and 15.6 Hz, 1H, H-9β), 2.95 (*ddd*, J = 5.1, 7.0 and 11.9 Hz, 1H, H-7), 4.42 (*d*, J = 1.2 Hz, 1H, H-15), 4.48 (*dt*, J = 1.2 and 5.1 Hz, 1H, H-8), 4.75 (*d*, J = 1.2 Hz, 1H, H-15'), 5.56 (*br.s.*, 1H, H-13) and 6.11 (*br.s.*, 1H, H-13'); ^{13}C NMR (Table 2).

11β-Phenylseleno-5,7αH,8βH-eudesm-3-en-8,12-olide (**14**).

From 145 mg (0.619 mmol) of compound **9** was obtained 166 mg (69%) of **14** by the procedure for preparation of **12**. Compound **14**: 140-142°C (hexane-ether); IR ν_{max} 3060, 3040, 2960-2840, 1760, 1435, 1380, 1220, 1010, 990, 735, 685 cm^{-1}; ^{1}H NMR δ 0.92 (*s*, 3H, H-14), 1.55 (*s*, 3H, H-13), 1.34 (*t*, J = 11.3 Hz, 1H, H-9α), 1.63 (*br.s.*, 3H, H-15), 1.76 (*dt*, J = 3.3 and 11.3 Hz, 1H, H-7), 2.02 (*dd*, J = 4.1 and 11.3 Hz, 1H, H-9β), 2.2-1.9 (*m*, 3H, overlapped signals of 2 H-2, H-5 and H-6), 4.61 (*dt*, J = 4.1 and 11.3 Hz, 1H, H-8), 5.35 (*br.s.*, 1H, H-3), 7.4-7.2 (*m*, 3H, aromatic) and 7.62 (*d*, J = 6.7 Hz, 2H , aromatic); ^{13}C NMR (Table 2).

11β-Phenylseleno-5,7,8αH-eudesm-3-en-8,12-olide (**15**).

From 110 mg (0.283 mmol) of compound **14**, was obtained 56 mg (51%) of **15**, along with 26 mg (23%) of starting product, by the procedure for preparation of **13**. Compound **15**: an oil; IR ν_{max} 3050, 2960-2840, 1760, 1440, 1375, 1080, 1220, 1160, 1080, 960, 840, 740, 690 cm^{-1}; ^{1}H NMR δ 0.88 (*s*, 3H, H-14), 1.36 (*dd*, J = 4.3 and 15.5 Hz, 1H, H-9α), 1.56 (*s*, 3H, H-13), 1.65 (*br.s.*, 3H, H-15), 2.13 (*dd*, J = 1.3 and 15.5 Hz, 1H, H-9β), 2.29 (*dd*, J = 6.0 and 12.2 Hz, 1H, H-5), 2.4-2.2 (*m*, 1H, H-7), 4.71 (*dt*, J = 1.3 and 4.3 Hz, 1H, H-8), 5.36 (*br.s.*, 1H, H-3), 7.4-7.2 (*m*, 3H, aromatic) and 7.79 (*dd*, J = 2.0 and 7.6 Hz, 2H, aromatic); ^{13}C NMR (Table 2).

5,7,8αH-Eudesma-3,11(13)-dien-8,12-olide or isoalloalantolactone (**2**).

From 52 mg (0.135 mmol) of compound **15** was obtained 23 mg (75 %) of isoalloalantolactone (**2**) by the procedure for preparation of isoalantolactone (**1**). Compound **2**: an oil; $[\alpha]_D^{25}$ +104° (c 1.05, $CHCl_3$); MS *m/e* 232 (0.7, M$^+$), 217 (16.5), 171 (7.9), 145 (8.3), 131 (10.2), 91 (35.7), 79 (34.2), 41 (100); HRMS 232.1465, $C_{15}H_{20}O_2$ requires 232.1458; IR ν_{max} 3000-2840, 1760, 1665, 1260, 1150, 1120, 950, 820, 800 cm^{-1}; ^{1}H NMR δ 0.87 (*s*, 3H, H-14), 1.23 (*ddd*, J = 6.5, 11.4 and 13.0 Hz, 1H, H-6β), 1.42 (*dd*, J = 4.8 and 15.6 Hz, 1H, H-9α), 1.59 (*br.s.*, 3H, H-15), 2.10-1.75 (*m*, 4H, overlapped signals of 2 H-2, H-6α, H-5), 2.12 (*dd*, J = 1.1 and 15.6 Hz, 1H, H-9β), 2.98 (*ddd*, J = 5.0, 7.2 and 11.4 Hz, 1H, H-7), 4.50 (*dt*, J = 1.1 and 5.0 Hz, 1H, H-8), 5.35 (*br.s.*, 1H, H-3), 5.57 (*br.s.*, 1H, H-13) and 6.10 (*br.s.*, 1H, H-13'); ^{13}C NMR (Table 2).

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