Functionality Transfer from C_6 to C_8 in Sesquiterpenes. Synthesis of 8-*epi*-Ivangustin and 8-*epi*-Isoivangustin from Santonin

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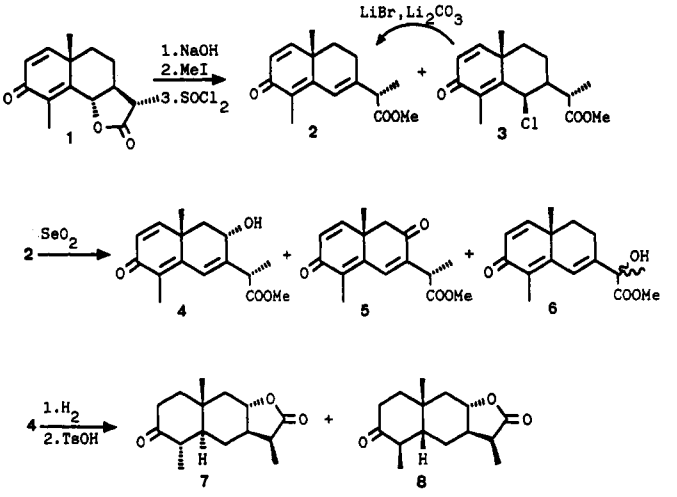
The short-range functionality transfer from C_6 to C_8 in eudesmane framework was reported. Santonin (1) was converted into 8-*epi*-ivangustin (16) and 8-*epi*-isoivangustin (18) via a synthetic pathway involving the aforementioned functionality transfer and treatment of an intermediate diselenide 9 with *m*-CPBA.

Eudesmane sesquiterpenes including both 6,12- and 8,12-olide moieties make up a group of natural compounds widely present in the plant kingdom.[1] These natural products have aroused much interest on account of their wide spectrum of biological properties, particularly the cytotoxic and antitumour activity associated with the α-methylene γ-lactone group.[2] Recent reports[3] also ascribe antifeedant properties to some sesquiterpene lactones. Numerous total and partial syntheses of this class of compounds have been published.[4] In continuation of our research on natural sesquiterpene lactones, we now report functionality transfer from C_6 to C_8 in eudesmanes and the synthesis of 8-*epi*-ivangustin (16) and 8-*epi*-isoivangustin (18) from santonin (1). Eudesmanolides 16 and 18 were first isolated by Bohlmann[5] from *Inula royleana* DC. and *Inula helenium* L. and later, together with some of its derivatives, from other plant material.[6] Synthesis of the 1-deoxy analogue of 16 from artemisin has been reported.[7]

The key to the C_8 functionalization of the eudesmane hydrocarbon skeleton was the trienone 2, which should allow the incorporation of an oxygen function at C_8 by allylic oxidation. This trienone was synthesized in two steps from the hydroxy carboxylate of santonin (1) by methylation of the carboxyl group with methyl iodide in *N,N*-dimethylformamide (DMF) and in situ dehydration of the hydroxyl group at C_6 by treatment with thionyl chloride in pyridine. Under strictly controlled reaction conditions[8] 2 was obtained in 62% yield, together with 10% of the chloride 3, which was subsequently subjected to elimination[9] with LiBr and Li_2CO_3 in DMF to yield the trienone 2 (88%). Therefore, the overall yield of 2 from santonin (1) was ca. 70%. This trienone had been previously synthesized by Yamakawa et al.[10] from santonin via a multistep pathway in 20% overall yield. Allylic oxidation of 2 with SeO_2 in dioxane[11] under reflux yielded ketol ester 4 (26% yield) together with the corresponding ketone 5 (3%), α-hydroxy ester 6 (18%), and 38% of unreacted trienone. The 8α-hydroxy configuration of compound 4 was determined from the coupling constants of H_8 (double doublet, J = 6.0 and 9.2 Hz). Attempts to increase the yield of 4 by varying the amount of oxidant (1.0–2.5 equiv), solvent (toluene, glyme, diglyme, THF, EtOH, AcOH), and reaction time (1–24 h) or using other oxidants (CrO_3/pyridine, lead tetraacetate, NBS) resulted in no significant improvements. Although the yield of 4 is relatively low, the fact that unreacted trienone can be recovered and efficiently recycled makes this reaction useful for functionalization at C8.

Once the oxygen function was transfered from C_6 in santonin to C_8, trienol 4 was hydrogenated catalytically

Scheme I



Scheme II

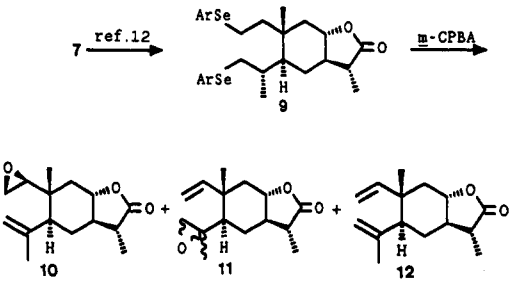


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Table I. ^{13}C NMR Data of Compounds 2–6, 10, 11, and 13–18 (δ, 50.3 MHz, $CDCl_3$)

	2[a]	3	4	5	6	10	11	13	14	15[b]	16	17[b]	18
C_1	154.6	157.1	154.6	153.8	154.9	58.8	147.2	77.3	75.7	77.2	77.2	75.6	75.7
C_2	127.0	125.1	127.0	126.9	127.0	44.5	111.8	31.8	32.6	31.8	31.7	32.6	32.7
C_3	186.5	186.2	186.4	185.2	186.6	114.8	56.1	26.7[c]	120.1	26.7[c]	26.8[c]	120.2	120.3
C_4	128.7[c]	133.8[c]	129.6[c]	135.0[c]	129.7[c]	144.6	57.0	130.4[d]	133.7	130.1[d]	129.8[d]	133.6	133.7
C_5	153.2[c]	153.4[c]	152.6[c]	148.9[c]	152.8[c]	50.1[c]	53.8[c]	127.3[d]	47.1	127.8[d]	127.9[d]	47.1	46.9[c]
C_6	121.9	59.4	123.2	136.6	120.9	28.9	26.0	27.6[c]	25.3	25.6[c]	26.0[c]	29.6	23.9
C_7	144.4[c]	44.8[d]	146.5[c]	140.2[c]	145.3[c]	51.6[c]	51.8[c]	51.7	52.6	56.0	48.8	57.1	50.0[c]
C_8	24.4	18.6	65.8	195.0	24.2	79.1	78.9	80.1	79.8	77.7	80.4	77.1	80.1
C_9	32.0	36.1	42.2	38.3	32.0	37.0	43.6	41.8	38.5	41.8	42.6	38.5	38.8
C_{10}	37.3	39.6	39.9	41.0	37.2	38.8	41.4[f]	41.6	40.3	41.6	41.6	40.3	
C_{11}	46.9	41.5[d]	41.9	47.1	76.4	41.3	41.4[f]	41.5	41.4	49.2	139.5	49.2	139.4
C_{12}	173.8	175.9	175.0	173.7	175.3	179.1	179.1	179.7	179.4	176.9	171.0	176.6	
C_{13}	15.7	16.0	15.4	15.6	21.8	12.4	12.5	12.5	12.5	22.5	117.3	22.6	117.0
C_{14}	24.9	27.6	25.6	27.0	24.6	23.6[d]	19.6[d]	19.2[e]	21.0[c]	19.2[e]	19.2[e]	21.0[c]	21.1[d]
C_{15}	9.9	10.3	10.1	10.6	10.1	16.7[d]	20.0[d]	19.6[e]	11.3[c]	19.7[e]	19.7[e]	11.3[c]	11.4[d]
CH_3O–	52.1	51.7	52.2	51.9	53.2								

[a] Assignment by heteronuclear ^1H–^{13}C correlation. [b] Aromatic carbons for 15 and 17: δ 138.2, 129.7, 129.1 and 124.3. [c–e] The signals with these superscripts may be interchanged within the corresponding spectrum. [f] Overlapped signals.

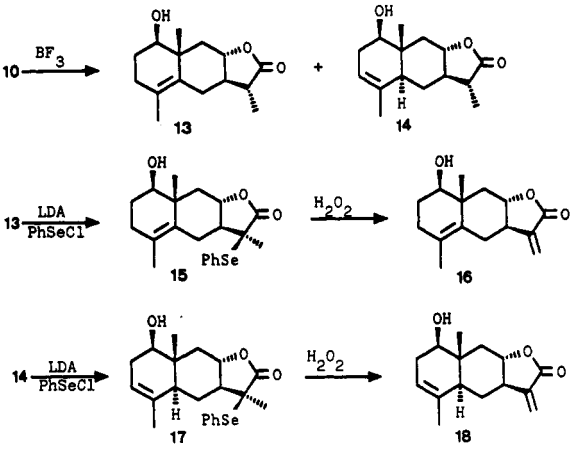
with carbon-supported palladium in acetone. Heating the crude hydrogenation mixture with benzene and *p*-toluenesulfonic acid yielded lactones **7** and **8**, which were separated by crystallization and column chromatography over silica gel. The trans-fused isomer **7** was obtained preferentially (51% yield) over the cis-fused isomer **8** (36% yield). In earlier work we synthesized **7** from artemisin and converted it in various natural 8,12-elemanolides[12] via the diselenide **9**. The conversion of **7** into **9** (22% overall yield) involves the formation of tosylhydrazone of **7**, a Shapiro reaction, ozonolysis followed by reduction with $NaBH_4$, and treatment of the diol thus obtained with (*o*-nitrophenyl)selenocyanate and tri-*n*-butylphosphine.[12] It is interesting to note that the stereochemistry at the lactone methyl group in diselenide **9** is opposite that in the compound **7** because in the Shapiro reaction the formation of the double bond was concomitant with an epimerization at C-11 as a result of the reprotonation of the lithium enolate of the lactone taking place at side β at 0 °C.[12]

In the present work we subjected diselenide **9** to various oxidation–elimination and epoxidation conditions in order to synthesize epoxyalkene **10**, a key intermediate for the synthesis of 8-*epi*-ivangustins. The fact that the elimination of the C_2 selenoxide should be faster[13] than that of the C_3 selenoxide led us to believe that epoxide **10** should be obtained preferentially over **11** to a greater extent than in the epoxidation of the divinyl compound **12** obtained by oxidation–elimination of diselenide **9** with H_2O_2. In fact, treatment of diselenide **9** with *m*-CPBA yielded both the divinyl compound **12** and the epoxides **10** and **11** in a 1.4:1 ratio, while direct epoxidation of **12** yielded epoxide **11** only.

Treatment of epoxide **10** with $BF_3{\cdot}OEt_2$ resulted in cyclization to the eudesmane skeleton giving a mixture of two isomers that were separated by HPLC. The less polar isomer was **14** (20% yield), as shown by its ^1H NMR spectrum [δ 5.29 (s, 1 H, H-3); 4.05 (dt, 1 H, J = 4.0 and 11.5 Hz, H-8β); 3.64 (dd, 1 H, J = 6.5 and 9.8 Hz, H-1α); 1.62 (s, 3 H, H-15)]. The more polar isomer (52% yield) was identified as **13** from its ^1H NMR spectrum [δ 4.07 (dt, 1 H, J = 3.7 and 11.5 Hz, H-8β); 3.56 (dd, 1 H, J = 7.1 and 8.7 Hz, H-1α); 1.60 (s, 3 H, H-15)].

Conversion of **13** and **14** into their corresponding *exo*-methylene derivatives **16** and **18** was accomplished via their phenylseleno derivatives **15** and **17**, which were synthesized

Scheme III



by reacting the lithium enolate with phenylselenyl chloride.[14] Oxidative syn elimination of **15** and **17** with 30% H_2O_2 yielded **16** and **18**, respectively. Their ^1H NMR spectra were quite consistent with their structures and identical with literature spectral data of natural 8-*epi*-ivangustin and 8-*epi*-isoivangustin, respectively.[5]

Experimental Section

All melting points are uncorrected. TLC was carried out on Merck 0.25-mm silica gel 60 HF_{254} analytical aluminum plates. Column chromatography separations were performed on silica gel (Merck, silica gel 60, 230–400 mesh). HPLC was carried out on a Konik KNK-500-A series using a S5W (Konik) column (25 cm × 10 mm i.d.). IR spectra were recorded as liquid films for oils and in KBr disk for solids. UV spectra were measured as solutions in MeOH. Specific rotations were measured as solution in $CHCl_3$. NMR spectra were run at 200.1 MHz for ^1H and 50.3 MHz for ^{13}C using $CDCl_3$ solutions. The carbon type (methyl, methylene, methine, or quaternary) was determined by DEPT experiments. Mass spectra were run by electron impact at 70 eV.

Methyl 3-Oxo-11β*H*-eudesma-1,4,6-trien-12-oate (2). To a solution of santonin **1** (5 g, 20 mmol) in 80% aqueous ethanol (260 mL) was added 1.5% aqueous NaOH (64 mL, 24 mmol) and the mixture stirred overnight until complete decolorization. The solvent was removed under reduced pressure to afford the hydroxy carboxylate, which was repeatedly dried by azeotropic distillation with benzene. To a solution of the resulting hydroxy carboxylate, in dry DMF (185 mL) at rt under Ar, was added, via syringe, methyl iodide (31.5 mL, 500 mmol), and the mixture was stirred for 30 min. The reaction mixture was cooled to 0 °C, and pyridine (185 mL) was added. Immediately, $SOCl_2$ (18.8 mL, 256 mmol)

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was added in two portions, quickly and with vigorous stirring. After 15 min the mixture reaction was heated at 70 °C for 1 h. Aqueous 5 M HCl (350 mL) was added and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with Na_2SO_3 solution and brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by chromatography of the residue (gradient elution, 5–40% hexane–ether) gave **2** (3.24 g, 62%) and **3** (0.59 g, 10%). Compound **2** had the following features: an oil, $[\alpha]^{22}_D$ 261° (*c* 5.7) [lit.[10b] $[\alpha]^{21}_D$ 273° (*c* 6.6)]; IR (NaCl) 1730, 1650, 1610, 825 cm^{-1}; UV λ_{max} 309.7 (ϵ = 12 200), 227.4 (ϵ = 12 500); MS *m/e* 260 (M^+, 70), 245 (M^+ – Me, 31), 201 (41), 185 (57), 173 (100), 128 (34); HRMS 260.1404, $C_{16}H_{20}O_3$ required 260.1407; ^1H NMR δ 6.65 (d, 1 H, *J* = 9.8 Hz, H-1), 6.15 (d, 1 H, *J* = 9.8 Hz, H-2), 6.45 (d, 1 H, *J* = 2.0 Hz, H-6), 3.62 (s, 3 H, CH_3O–), 3.23 (q, 1 H, *J* = 7.1 Hz, H-11), 2.39 (dddd, 1 H, *J* = 2.0, 5.9, 11.5, 18.8 Hz, H-8β), 2.17 (dd, 1 H, *J* = 6.1, 18.8 Hz, H-8α), 2.08 (d, 3 H, *J* = 7.1 Hz, H-13), 1.87 (s, 3 H, H-15), 1.72 (ddd, 1 H, *J* = 1.5, 5.9, 13.0 Hz, H-9β), 1.52 (ddd, 1 H, *J* = 6.0, 11.5, 13.0 Hz, H-9α), 1.31 (d, 3 H, *J* = 7.2 Hz, H-13), 1.08 (s, 3 H, H-14). Compound **3** had the following features: mp 70–72 °C (from hexane–CH_2Cl_2); $[\alpha]^{22}_D$ –152° (*c* 0.63); IR (KBr) 1725, 1645, 1620, 840 cm^{-1}; MS *m/e* 298 and 296 (M^+, 3 and 9), 261 (M^+ – Cl, 25), 260 (M^+ – HCl, 17), 201 (33), 185 (34), 173 (100); HRMS 296.1168, $C_{16}H_{21}O_3Cl$ required 296.1174; ^1H NMR δ 6.64 (d, 1 H, *J* = 9.8 Hz, H-1), 6.15 (d, 1 H, *J* = 9.8 Hz, H-2), 5.34 (d, 1 H, *J* = 3.0 Hz, H-6), 3.68 (s, 3 H, CH_3O–), 2.73 (quint, 1 H, *J* = 7.2 Hz, H-11), 1.93 (s, 3 H, H-15), 1.9–1.7 (m, 5 H, H-7, H-8, H-9), 1.41 (s, 3 H, H-14), 1.21 (d, 3 H, *J* = 7.2 Hz, H-13).

Methyl 3-Oxo-11β*H*-eudesma-1,4,6-trien-12-oate (2) from 3. A suspension of chloride **3** (488 mg, 1.65 mmol), Li_2CO_3 (350 mg), and LiBr (256 mg) in DMF (19 mL) was heated at 120 °C for 45 min. The reaction was quenched with saturated aqueous NH_4Cl solution (40 mL) and extracted with ethyl acetate. Usual workup yielded 378 mg of compound **2** (88%).

Methyl 8α-Hydroxy-3-oxo-11β*H*-eudesma-1,4,6-trien-12-oate (4). A solution containing 1.757 g (6.93 mmol) of compound **2** and 0.972 g of SeO_2 in 60 mL of dry dioxane was refluxed, under argon, for 2 h. The reaction mixture was filtered through a pad of Kieselguhr, and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane–ethyl acetate) to give 674 mg (38%) of unconsumed **2**, 57 mg (3%) of diketone **5**, 333 mg (18%, 29% based on consumed **2**) of α-hydroxy ester **6**, and 485 mg (26%, 42% based on consumed **2**) of ketol ester **4**. Compound **5** had the following features: mp 123–125 °C (hexane–CH_2Cl_2) (lit.[10a] mp 127.5–129 °C); $[\alpha]^{22}_D$ 251° (*c* 3.5) [lit.[10a] $[\alpha]^{22}_D$ 256° (*c* 1.66)]; IR (KBr) 1737, 1672, 1645, 1620, 1210 cm^{-1}; UV λ_{max} 310.3 (ϵ = 17 410), 201.1 (ϵ = 19 900) nm; MS *m/e* 274 (M^+, 61), 259 (M^+ – Me, 28), 242 (M^+ – MeOH, 55), 227 (23), 215 (77), 214 (100), 200 (35), 199 (44), 107 (37); HRMS: 274.1197, $C_{16}H_{18}O_4$ required 274.1200; ^1H NMR δ 7.45 (s, 1 H, H-6), 6.76 (d, 1 H, *J* = 9.8 Hz, H-1), 6.20 (d, 1 H, *J* = 9.8 Hz, H-2), 3.74 (q, 1 H, *J* = 7.3 Hz, H-11), 3.66 (s, 3 H, CH_3O–), 2.61 and 2.42 (each d, 1 H each, *J* = 15.9 Hz, H-9), 2.11 (s, 3 H, H-15), 1.40 (d, 3 H, *J* = 7.3 Hz, H-13), 1.32 (s, 3 H, H-15). Compound **6**: an oil; $[\alpha]^{22}_D$ 169° (*c* 1.4); IR (NaCl) 3500–3300, 1730, 1645, 1600, 825 cm^{-1}; UV λ_{max} 309.4 (ϵ = 11 640), 227.4 (ϵ = 10 730) nm; MS *m/e* 276 (M^+, 5), 258 (M^+ – H_2O, 48), 218 (14), 217 (100), 202 (11), 189 (13), 159 (11); HRMS: 276.1350; $C_{16}H_{20}O_4$ required 276.1356; ^1H NMR δ 6.82 (d, 1 H, *J* = 2.2 Hz, H-6), 6.72 (d, 1 H, *J* = 9.8 Hz, H-1), 6.23 (d, 1 H, *J* = 9.8 Hz, H-2), 3.80 (s, 3 H, CH_3O–), 2.54 (dd, 1 H, *J* = 5.9, 18.8 Hz, H-8α), 2.17 (dddd, 1 H, *J* = 2.2, 5.9, 11.5, 18.8 Hz, H-8β), 1.95 (s, 3 H, H-15), 1.79 (ddd, 1 H, *J* = 1.2, 5.9, 13.2 Hz, H-9β), 1.63 (s, 3 H, H-13), 1.57 (ddd, 1 H, *J* = 5.9, 11.5, 13.2 Hz, H-9α), 1.11 (s, 3 H, H-14). Compound **4**: mp 110–112 °C (ether); $[\alpha]^{22}_D$ 143° (*c* 0.35); IR (KBr) 3390, 1730, 1640, 1620, 1600, 1050, 840, 825 cm^{-1}; UV λ_{max} 305.1 (ϵ = 18 000), 227.3 (ϵ = 12 120) nm; MS *m/e* 261 (M^+ – Me, 16), 244 (M^+ – MeOH, 21), 229 (23), 216 (15), 201 (36), 189 (100), 174 (31), 173 (31); HRMS 261.1115, $C_{15}H_{17}O_4$ (M^+ – Me) required 261.1122; ^1H NMR δ 6.74 (d, 1 H, *J* = 9.8 Hz, H-1), 6.57 (s, 1 H, H-6), 6.25 (d, 1 H, *J* = 9.8 Hz, H-2), 4.56 (dd, 1 H, *J* = 6.0, 9.2 Hz, H-8β), 3.71 (s, 3 H, CH_3O–), 3.67 (q, 1 H, *J* = 7.3 Hz, H-11), 2.25 (dd, 1 H, *J* = 6.0, 12.5 Hz, H-9β), 1.96 (s, 3 H, H-15), 1.51 (dd, 1 H, *J* = 9.2, 12.5 Hz, H-9α), 1.47 (d, 3 H, *J* = 7.3 Hz, H-13), 1.14 (s, 3 H, H-14).

3-Oxo-5,7,11α*H*,4,8β*H*-eudesman-8,12-olide (7) and 3-Oxo-4,7,11α*H*,5,8β*H*-eudesman-8,12-olide (8). A solution of 1.62 g (5.89 mmol) of hydroxy ester **4** in 35 mL of acetone was hydrogenated over a 5% Pd/C catalyst (408 mg). After being stirred at rt for 1 h, an additional amount of catalyst (408 mg) was added and the suspension was stirred for 2.5 h. After removal of the catalyst by filtration through a pad of silica gel, the filtrate was concentrated in vacuo. A solution of the oily residue and *p*-toluenesulfonic acid (in a catalytic amount) in 120 mL of dry benzene was heated under reflux for 1.5 h. The reaction mixture was filtered through silica gel, and the filtrate was concentrated in vacuo. By crystallization (hexane–CH_2Cl_2), 718 mg of compound **7** (mp 189–190 °C) was obtained. Careful chromatography (CH_2Cl_2–isobutyl alcohol in ratios of 100:0–100:0.3) of the liquors mothers gave 114 mg of compound **7** (51% total yield) and 587 mg of compound **8** (36%) (mp 99–100 °C, for hexane–CH_2Cl_2). For physical and chemical features of compounds **7** and **8**, see ref 12.

2,3-Bis[(*o*-nitrophenyl)seleno]-5,7α*H*,4,8,11β*H*-eleman-8,12-olide (9). See ref 12.

1,2β-Epoxy-5,7α*H*,8,11β*H*-elem-3-en-8,12-olide (10). To a solution containing 88 mg (0.14 mmol) of diselenide **9** in CH_2Cl_2 (3.3 mL) was added 85% *m*-CPBA (210 mg, 1.05 mmol), and the resulting mixture was stirred at 0–4 °C for 8 days. The mixture was diluted with CH_2Cl_2 and was washed with 5% aqueous Na_2CO_3 solution and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The reaction product was chromatographed on silica gel (hexane–ether) to afford 5.5 mg (17%) of compound **12**, 12.5 mg (34%) of compound **10**, and 8.5 mg (24%) of **11**. For spectral features of compound **12**, see ref 12. Compound **10**: an oil; $[\alpha]^{22}_D$ 15° (*c* 0.3); IR (NaCl) 3070, 1770, 1635, 1000, 900 cm^{-1}; MS *m/e* 235 (M^+ – Me, 2), 207 (2), 165 (4), 137 (4), 123 (5), 93 (25), 68 (100); HRMS 235.1524, $C_{14}H_{19}O_3$ (M^+ – Me) required 235.1329; ^1H NMR δ 4.98 and 4.94 (each s, 1 H each, H-3), 3.95 (ddd, 1 H, *J* = 4.0, 10.0, 12.0 Hz, H-8β), 2.88 (t, 1 H, *J* = 3.5 Hz, H-1), 2.67 (d, 2 H, *J* = 3.5 Hz, H-2), 2.32 (dd, 1 H, *J* = 3.5, 11.5 Hz, H-5), 2.30 (dq, 1 H, *J* = 6.8, 12.0 Hz, H-11), 1.9–1.8 (m overlapped with H-9β, H-6β), 1.86 (dd, 1 H, *J* = 4.0, 11.7 Hz, H-9β), 1.78 (s, 3 H, H-15), 1.63 (q, 1 H, *J* = 11.8 Hz, H-6β), 1.6–1.4 (m, overlapped with H-6β and H-9α, H-7), 1.56 (dd, *J* = 11.7, 12.0 Hz, H-9α), 1.20 (d, 3 H, *J* = 6.8 Hz, H-13), 0.95 (s, 3 H, H-14). Compound **11**: an oil; $[\alpha]^{22}_D$ –21° (*c* 1.37); IR (NaCl) 3080, 1770, 1652, 1000, 900 cm^{-1}; MS *m/e* 235 (M^+ – Me, 12), 207 (4), 165 (7), 137 (14), 123 (19); HRMS 235.1325, $C_{14}H_{19}O_3$ (M^+ – Me) required 235.1329; ^1H NMR δ 5.80 (dd, 1 H, *J* = 10.8, 17.4 Hz, H-1), 5.02 (d, 1 H, *J* = 17.4 Hz, H-2), 5.01 (d, 1 H, *J* = 10.8 Hz, H-2′), 3.93 (dt, 1 H, *J* = 4.0, 10.3 Hz, H-8β), 2.68 and 2.58 (each d, 1 H, each, *J* = 4.3 Hz, H-3), 2.30 (dq, 1 H, *J* = 7.0, 12.0 Hz, H-11), 2.04 (dd, 1 H, 3.5, 9.5 Hz, H-5), 1.9–1.7 (m, overlapped with H-9β, H-6β), 1.86 (dd, *J* = 4.0, 11.7 Hz, H-9β), 1.7–1.4 (m, overlapped with H-9α, H-6α, H-7), 1.55 (dd, *J* = 10.3, 12.0, H-9α), 1.21 (s, 3 H, H-15), 1.19 (d, 3 H, *J* = 7.0 Hz, H-13), 1.18 (s, 3 H, H-14).

1β-Hydroxy-7α*H*,8,11β*H*-eudesm-4-en-8,12-olide (13) and 1β-Hydroxy-7α*H*,8,11β*H*-eudesm-3-en-8,12-olide (14). To a solution of **10** (59 mg, 0.23 mmol) in benzene (4 mL) was added BF_3·Et_2O (0.064 mL, 0.24 mmol). The mixture was stirred at rt for 15 min, after which it was diluted with EtOAc and was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Preparative HPLC (hexane–ethyl acetate (6:4)) separated 12 mg (20%) of **14** and 31 mg (52%) of **13**. Compound **13**: an oil; $[\alpha]^{22}_D$ 61.8 (*c* 6.7); IR (NaCl) 3500–3300, 1755, 1640, 1000 cm^{-1}; MS *m/e* 250 (M^+, 11), 235 (M^+ – Me, 3), 232 (M^+ – H_2O, 19), 217 (29), 206 (30), 120 (100), 119 (36), 107 (29), 105 (51), 95 (27), 91 (47); HRMS 250.1558, $C_{15}H_{22}O_3$ required 250.1563; ^1H NMR δ 4.07 (dt, 1 H, *J* = 3.7, 11.5 Hz, H-8β), 3.56 (dd, 1 H, *J* = 7.1, 8.7 Hz, H-1α), 2.78 (dd, 1 H, *J* = 3.4, 13.9 Hz, H-6α), 2.51 (dd, 1 H, *J* = 3.7, 11.5 Hz, H-9β), 2.31 (dq, 1 H, *J* = 7.1, 11.8 Hz, H-11), 2.2–2.0 (m, 2 H, H-3), 1.83 (t, 1 H, *J* = 13.9 Hz, H-6β), 1.8–1.6 (m, 2 H, H-2), 1.60 (s, 3 H, H-15), 1.44 (dq, 1 H, *J* = 3.5, 12.0 Hz, H-7), 1.30 (t, 1 H, *J* = 11.5 Hz, H-9α), 1.21 (d, 3 H, *J* = 7.1 Hz, H-13), 1.07 (s, 3 H, H-14). Compound **14**: mp 142–144 °C (hexane–EtOAc); $[\alpha]^{22}_D$ –13.4 (*c* 2.7); IR (KBr) 3495, 1745, 1630, 995 cm^{-1}; MS *m/e* 250 (M^+, 19), 232 (M^+ – H_2O, 11), 217 (6), 180 (23), 177 (11), 81 (100), 95 (21); HRMS 250.1561, $C_{15}H_{22}O_3$ required 250.1563; ^1H NMR δ 5.29 (s, 1 H, H-3), 4.05 (dt, 1 H, *J* = 4.0, 11.5 Hz, H-8β), 3.64 (dd, 1 H, *J* = 6.5, 9.8 Hz, H-1α), 2.5–2.3 (m, overlapped with H-9β and H-11,

H-2'), 2.44 (dd, 1 H, J = 4.0, 11.5 Hz, H-9β), 2.32 (dq, 1 H, J = 7.2, 12.0 Hz, H-11), 2.1–2.0 (m, 3 H, H-2, H-5 and H-6α), 1.62 (s, 3 H, H-15), 1.51 (dq, 1 H, J = 3.0, 11.5 Hz, H-7), 1.30 (m, overlapped with H-9α and H-13, H-6β), 1.27 (t, 1 H, J = 11.5 Hz, H-9α), 1.27 (d, 3 H, J = 7.2 Hz, H-13), 0.87 (s, 3 H, H-14).

1β-Hydroxy-11β-(phenylseleno)-7α*H*,8α*H*-eudesm-4-en-8,12-olide (15). To a THF solution of lithium diisopropylamide prepared from 0.041 mL (0.29 mmol) of diisopropylamine, 1.6 M *n*-BuLi in hexane (0.18 mL, 0.28 mmol), and 0.4 mL of dry THF at −78 °C was added 23 mg (0.095 mmol) of compound **13** in 0.4 mL of dry THF. After the solution was stirred at −78 °C for 1 h, 56 mg (0.28 mmol) of phenylselenyl chloride in 0.8 mL of dry THF and 45 μL of HMPA were added at −78 °C. The mixture was stirred at the same temperature for 1 h then warmed to −30 °C and kept at this temperature for 2 h. The reaction was quenched by adding 1 mL of 10% HCl at 0 °C. The product was treated as usual[12] and chromatographed on silica gel to give 25 mg (65%) of compound **15**, with the following features: an oil; IR (NaCl) 3500–3300, 3070, 1755, 730 cm^{-1}; ^{1}H NMR δ 7.62 (dd, 1 H, J = 1.3, 7.8 Hz, aromatic), 7.5–7.3 (m, 3 H, aromatic), 4.53 (dt, 1 H, J = 4.2, 11.5 Hz, H-8β), 3.55 (dd, 1 H, J = 6.2, 9.6 Hz, H-1α), 2.76 (dd, 1 H, J = 3.3, 13.7 Hz, H-6α), 2.53 (dd, 1 H, J = 4.2, 11.5 Hz, H-9β), 2.2–2.0 (m, 3 H, H-3 and H-6β), 1.9–1.6 (m, 3 H, H-2 and H-7), 1.63 (s, 3 H, H-15), 1.53 (s, 3 H, H-13), 1.29 (t, 1 H, J = 11.5 Hz, H-9α), 1.06 (s, 3 H, H-14).

1β-Hydroxy-7α*H*,8β*H*-eudesma-4,11(13)-dien-8,12-olide (16). To a solution containing 17.5 mg (0.043 mmol) of compound **15** in 0.45 mL of THF cooled to 0 °C was added 11 μL (0.106 mmol) of 30% H_2O_2. The mixture was stirred at rt for 1 h and then poured into brine. The usual procedure yielded 8.5 mg (76%) of compound **16** with the following features: an oil, $[\alpha]^{22}_D$ −26.4° (*c* 0.41) [lit.[5] $[\alpha]^{24}_D$ −25.4° (*c* 3.7)]; IR (NaCl) 3500–3300, 1765, 1630, 1005 cm^{-1}; MS *m/e* 248 (M^+, 14), 230 ($M^+ - H_2O$, 17), 215 (30), 204 (44), 189 (32), 162 (28), 161 (21), 120 (100), 94 (52), 91 (51); HRMS 248.1403, $C_{15}H_{20}O_3$ required 248.1407; ^{1}H NMR δ 6.09 and 5.42 (each d, 1 H each, J = 3.1 Hz, H-13), 4.07 (dt, 1 H, J = 3.4, 11.6 Hz, H-8β), 3.61 (t, 1 H, J = 8.0 Hz, H-1α), 2.98 (dd, 1 H, J = 3.1, 13.9 Hz, H-6α), 2.56 (dd, 1 H, J = 3.4, 11.6 Hz, H-9β), 2.4–2.1 (m, 1 H, H-7) 1.93 (t, 1 H, J = 13.9 Hz, H-6β), 1.8–1.6 (m, 2 H, H-2), 1.65 (s, 3 H, H-15), 1.38 (t, 1 H, J = 11.6 Hz, H-9α), 1.06 (s, 3 H, H-14).

1β-Hydroxy-11β-(phenylseleno)-5,7α*H*,8β*H*-eudesm-3-en-8,12-olide (17). From 7 mg (0.028 mml) of compound **14** was obtained 8.5 mg (73%) of **17** by the procedure for preparation of **15**. Compound **17**: an oil; IR (NaCl) 3500–3300, 3075, 1745, 730, 675 cm^{-1}; ^{1}H NMR δ 7.62 (dd, 1 H, J = 1.3, 7.9 Hz, aromatic), 7.4–7.2 (m, 3 H, aromatic), 5.31 (s, 1 H, H-3), 4.56 (dt, 1 H, J = 4.0, 11.5 Hz, H-8β), 3.64 (dd, 1 H, J = 6.8, 9.6 Hz, H-1α), 2.5–2.3 (m, overlapped with H-9β, H-2α), 2.48 (dd, 1 H, J = 4.0, 11.5 Hz, H-9β), 2.04 (br, d, 1 H, H-5) 2.00 (dd, 1 H, J = 9.6, 11.9 Hz, H-2β), 1.75 (dt, 1 H, J = 3.0, 11.5 Hz, H-7), 1.67 (s, 3 H, H-15), 1.55 (s, 3 H, H-13), 0.90 (s, 3 H, H-14).

1β-Hydroxy-5,7α*H*,8β*H*-eudesma-3,11(13)-dien-8,12-olide (18). From 8.5 mg (0.021 mmol) of compound **17** was obtained 4 mg (74%) of **18** by the procedure for preparation of **16**. Compound **18**: mp 135–137 °C (hexane–ether) (lit.[5] mp 135.5 °C); $[\alpha]^{22}_D$ −66 (*c* 0.01) [lit.[5] $[\alpha]^{24}_D$ −50.4 (*c* 0.41)]; IR (NaCl) 3520, 1745, 1140, 995 cm^{-1}; MS *m/e* 248 (M^+, 9), 230 ($M^+ - H_2O$, 5), 215 (4), 178 (34), 149 (8), 121 (8), 93 (11), 91 (15), 82 (35), 81 (100); HRMS 248.1404, $C_{15}H_{20}O_3$ required 248.1407; ^{1}H NMR δ 6.07 and 5.42 (each d, 1 H each, J = 3.1 Hz, H-13), 5.33 (s, 1 H, H-3), 4.03 (dt, 1 H, J = 4.0, 11.5 Hz, H-8β), 3.68 (t, 1 H, J = 9.1 Hz, H-1α), 2.49 (dd, 1 H, J = 3.9, 11.9 Hz, H-9β), 2.39 (dd, 1 H, J = 3.0, 7.5 Hz, H-2α), 2.15 (d, 1 H, J = 3.3, 12.5 Hz, H-5), 2.1–2.0 (m, 1 H, H-2β), 1.67 (s, 3 H, H-15), 1.40 (m, 2 H, H-6β and H-9α), 0.87 (s, 3 H, H-14).

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Supplementary Material Available: ^{13}C NMR spectra of compounds **2–6**, **10**, **11**, and **13–18** (13 pages). Ordering information is given on any current masthead page.