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SYNTHESIS OF VARIOUS NATURAL 8,12-ELEMANOLIDES FROM ARTEMISIN

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Abstract.– This paper describes the chemical transformations of artemisin into various natural 8,12-elemanolides.

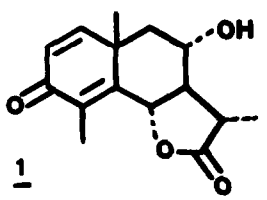
In earlier work, the authors used artemisin (1) to prepare various sesquiterpenic lactones[1,2] including some bearing the α-methylene-γ-lactone grouping. This group of natural products has aroused great interest of the medical sciences on account of its peculiar biological properties —they are chiefly used as cytostatic, antitumour and bactericidal agents.[3] Recent reports also attribute anti-feedant properties to some sesquiterpenic lactones, which would allow their use as indirect insecticides.[4]

This paper reports on the chemical transformations of artemisin (1) into 8,12-elemanolides (2) and (3). The former elemanolide was first isolated by Bohlmann from *Liatris platylepis*[5] and later from *Spilanthes leiocarpa*[6] and *Critonia quadrangularis*.[7] Structure (3) represents no natural product as, though originally assigned to an elemanolide isolated from *Liatris platylepis*,[5] *Liatris cylindracea*[8] and *Eupatorium quadrangulare*,[9] it was later rectified.[6,7] 8,12-Elemanolide (2) was recently synthesized[10] in racemic form.

Artemisin is a very suitable starting material for the synthesis of 8,12-elemanolides insofar as it has the same configuration at C_7 and C_{10}, and an oxygenated function at C_8. As the total synthesis of this compound was achieved elsewhere,[11,12] that described here can be formally considered as such.

RESULTS AND DISCUSSION

The reductive cleavage of the C_6–O bond is a key step in the conversion of the 6,8-olide group of artemisin into the 8,12-olide function of elemanolides (2) and (3). Such a conversion, which was described elsewhere[13], involves two reactions. In the first takes place the epimerization at C_6, which is effected with HCl/DMF. The configurational change at C_6 was readily observed in the ^{1}H NMR spectrum [a doublet at δ 4.79 for H-6 with J = 11.5 Hz in artemisin (1), and another doublet at δ 5.61 with J = 4.8 Hz in 6-epiartemisin (4)]. In the second reaction, 6-epiartemisin (4) is converted to acid (5a) upon treatment with Zn



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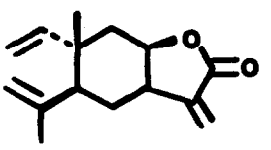

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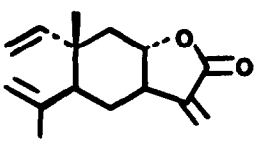

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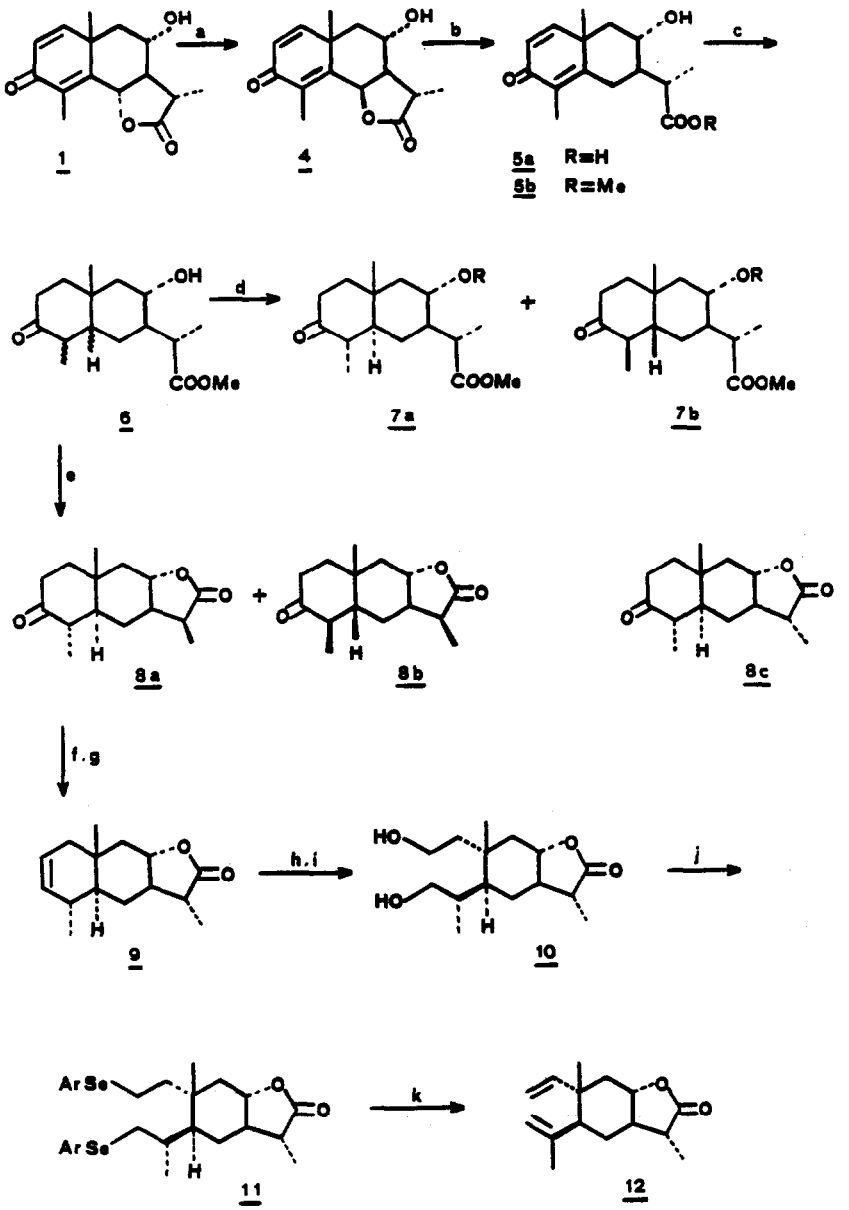
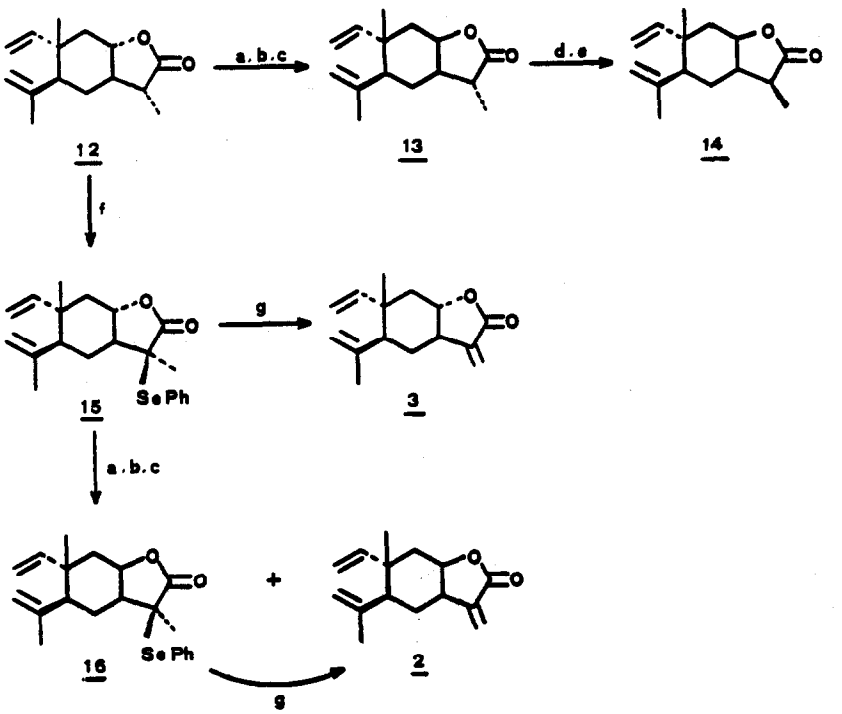
dust activated in methanol under reflux; the acid was not isolated as such, but as its methyl ester (5b). The methylation was carried out by filtering the Zn out, adding methanol and a catalytic amount of concentrated H_2SO_4 and heating under reflux. The yield (77%) was somewhat higher than that reported elsewhere[13] (64%). For practical reasons, it is advisable to effect the reductive cleavage of the C_6–bond from the epimerization mixture as the unreacted starting artemisin does not further react with Zn and hence makes the chromatographic separation of the final mixture easier than that of the epimerization mixture.

The following stage involved the catalytic hydrogenation with Pd/C of the dienonic system of (5b). The crude mixture of tetrahydro derivatives (6) was treated with *t*-butyldimethylsilyl chloride in DMF/imidazole[14] in order to protect the hydroxyl group at C_8, epimerize the C_4–Me group and, particularly, facilitate the chromatographic separation of the stereoisomers according to our previous experience.[1] However, it was impossible to separate isomers (7a) and (7b) in this case; hence, the crude mixture of tetrahydro derivatives (6) was heated with benzene and *p*-toluenesulphonic acid under reflux, which caused their epimerization at C_4 and lactonization at C_8 to yield products (8a) and (8b), which were separated by column chromatography over silica gel (100:0.2 CH_2Cl_2–isobutyl alcohol). The major product obtained was the *trans*-fused isomer (8a), with a yield of 44%, while the *cis*-fused isomer (8b) was obtained with a yield of 28%. Both stereoisomers gave a dual triplet at δ 4.38 corresponding to H-8, whereas the signal of this proton appeared at δ 3.99 in the starting product.

The next step involved the formation of a double $\Delta^{2,3}$ bond, which was accomplished through a Shapiro reaction.[15] The tosylhydrazone of (8a) was converted into olefin (9) upon treatment with lithium diisopropylamide in THF at –78°C. 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. Thus, while carbon C_{13} gave a signal at δ 9.5 in the starting ketolactone (8a), such a signal appeared at δ 12.5 in the olefin obtained. In order to confirm this fact, ketolactone (8a) was treated directly with LDA in THF at –78°C and reprotonated at 0°C; the product obtained was ketolactone (8c), whose C_{13} carbon yielded a signal at δ 12.5, identical with that of olefin (9). This olefin treated, with ozone at –78°C, followed by reduction with $NaBH_4$, yielded diol (10), which gave ^{1}H NMR signals at δ 3.3–3.5 for $2H_3$ and δ 3.6–3.8 for $2H_2$. The conversion of (10) into its corresponding divinyl system (12) was accomplished in two steps through di-*o*-nitrophenylselenide (11), which was obtained with a 93% yield by treatment of diol (10) with *o*-nitrophenylselenocyanate[16] and tri-n-butylphosphine in THF. Thus, for this 8,12-elemanolide, the yield of the di-*o*-nitrophenylselenide, unlike with 6,12-elemanolides, in which the diselenide is obtained with the monoselenide[1] or is not obtained at all,[17] was excellent. The oxidative elimination of (11) was carried out with hydrogen peroxide, which yielded the divinyl compound (12). Consistent with its structure, its ^{1}H and ^{13}C NMR spectra showed the typical signals of vinyl groups,[18] namely at δ 148.1, 111.1, 113.9 and 145.2 for C_1, C_2, C_3 and C_4, respectively. Product (12) was converted into the natural elemanolide[7] (14) upon epimerization at C_8 and C_{11}. The epimerization at C_8 was effected according to the Lansbury method,[19] by saponifying (12), treating the potassium salt thus obtained with excess mesyl chloride and triethylamine in THF and adding aqueous hydroxide. The epimerization mixture contained about 50% of *cis*-lactone (13) (quadruplet at δ 4.67, with J = 4.0 Hz, for H-8, while *trans*-lactone (12) gave a double doublet at δ 3.98, with J = 3.9, 10.0 and 12.0 Hz). The epimerization of product (13) at C_{13} was accomplished by reprotonation of the lithium enolate of the lactone with *t*-butyl alcohol[10] at –110°C. Carbon C_{11} gave a signal at δ 14.3 in product (13) and at δ 9.2 in its epimer (14).



Reagents: (a) HCl/DMF; (b) Zn/MeOH; (c) H_2, Pd/C; (d) TMDSCl, imidazole; (e) *p*-TsOH/benzene; (f) $TsNHNH_2$, $BF_3{\cdot}OEt_2$; (g) LDA; (h) O_3; (i) $NABH_4$; (j) ArSeCN, n-Bu_3P; (k) 30% H_2O_2. R = TBDMS–; Ar = *o*-$NO_2C_6H_4$–.



Reagents: (a) NaOH; (b) CH_3SO_2Cl, Et_3N; (c) NaOH; (d) LDA; (e) *t*-BuOH (–110°C); (f) LDA, PhSeCl; (g) 30% H_2O_2.

The conversion of (12) and (13) into their corresponding *exo*-methylene derivatives (3) and (2) was effected through their phenylseleno derivatives.[20] In both cases, the phenylselenyl group must have a β orientation in order to achieve the *syn*- elimination of the selenoxide with the required regiospecificity. As the attack of the selenylizing agent takes place at the less hindered α side in *cis*-fused lactones, (2) and (3) were synthesized from (12). Thus, by reacting the lithium enolate of (12) with phenylselenyl chloride, we obtained compound (15), which yielded (3) upon oxidative *syn*-elimination with hydrogen peroxide. Its structure was consistent with the ^{1}H NMR spectrum obtained (doublets at δ 5.39 and 6.06 for $=CH_2$, among other signals). On the other hand, the epimerization of phenylselenolactone (15) at C_8 was accomplished by the Lansbury method,[19] the application of which yielded a mixture of unreacted starting product (15) (30%), phenylselenolactone (16) (13%) and *exo*-methylenelactone (2) (33%). It is interesting to note that, under the conditions used in the epimerization reaction, phenylselenolactone (16) underwent the elimination reaction relatively easily, which was not the case with its C_{11}-epimer (15). Finally, phenylselenolactone (16) was converted into *exo*-methylenelactone (2) through oxidation with hydrogen peroxide and elimination. Structure (2) is quite consistent with the ^{1}H NMR spectrum obtained (signals at δ 5.56 and 6.16, doublets for $=CH_2$ and δ 4.55, triplet for H-8α, among others).

Table 1 ^{13}C NMR data of compounds (4)–(11) (50.3 MHz, $CDCl_3$, δ values)

	(4)	(5b)[c]	(8a)	(8b)	(8c)	(9)	(10)	(11)[d]
C_1	125.5	125.8	37.1	35.7*	37.1	44.1	43.9	19.9
C_2	156.6	155.4	44.2	37.3	43.9	123.5[a]	58.0[a]	34.5[a]
C_3	185.9	186.1	211.2	212.7	211.1	132.7[a]	66.8[a]	40.1[a]
C_4	147.4	157.5	47.8	43.1[a]	51.0	47.9	41.8	47.5
C_5	137.9	129.6	38.7	38.5	41.4	32.8	33.1	29.9
C_6	77.0	28.2	24.6	22.6	27.1	27.0	23.6	23.8
C_7	51.2	48.4	38.7	49.4	52.0	52.1	51.6	51.6
C_8	66.4	66.4	77.7	78.5	78.9	79.5	80.0	79.3
C_9	42.4	45.2	40.2	41.1	40.4	41.7	41.7	41.4
C_{10}	40.1	40.2	35.9	35.7*	36.1	34.9	38.8	40.3
C_{11}	41.2	39.3	44.9	40.8[a]	45.0	41.4	41.5	41.5
C_{12}	179.4	176.0	179.7	–	179.1	179.5	179.9	179.1
C_{13}	11.1[a]	10.4[a]	9.5	9.2	12.5	12.5	12.4	12.5
C_{14}	14.9[a]	13.3[a]	11.6[a]	12.0[b]	11.7[a]	18.7[b]	13.7[b]	18.1[b]
C_{15}	25.6	24.4	17.9[a]	28.3[b]	17.9[a]	19.3[b]	22.8[b]	21.6[b]

[a,b] Chemical shits denoted by the same letter in each column are interchangeable

[c] CH_3O– for compound (5b): 51.6

[d] Aromatic carbons for compound (11): 125.4, 125.6, 126.3, 126.5, 128.6, 128.7, 131.2, 131.4, 133.6, 133.7, 146.3 and 146.7

* Overlapped signals

EXPERIMENTAL

Melting points were determined in capillary tubes with a Büchi melting point apparatus and were used uncorrected. IR spectra were recorded on a Perkin-Elmer 281 spectrometer, while NMR spectra were run on a Brucker AC-200 instrument (200.1 MHz for ^1H and 50.3 MHz for ^{13}C) by using $CDCl_3$ solutions. Mass spectra were recorded at 70 eV on a Varian MAT-311A spectrometer.

6-Epiartemisin (4)

One gramme (3.8 mmol) of artemisin (1) was dissolved in 15 mL of dry DMF containing 5% HCl. The solution was heated under argon at 85–90°C for 4 h, then poured into water and extracted with CH_2Cl_2. The combined organic layer was next washed with saturated aqueous $NaHCO_3$ and water, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The reaction product was chromatographed on silica gel with hexane–EtOAC and yielded 0.57 g (57%) of 6-epiartemisin (4). Unreacted artemisin (60 mg) was recovered. Compound (4) had the following features: m.p. 159–160°C (hexane-CH_2Cl_2) (lit.[21] m.p. 156–157°C); IR ν_{max} : 3480, 3060, 3000–2880, 1770, 1670, 1640, 1080, 860 cm^{-1}; ^1H NMR δ: 1.29 (s, H-14), 1.42 (d, J = 7.5 Hz, H-13), 1.4–1.6 (m. overlapped with H-13, H-9α), 1.9–2.1 (m. overlapped with H-15, H-9β and H-7), 2.05 (s, H-15), 2.99 (q, J = 7.5 Hz, H-11), 3.0–3.1 (broad signal overlapped with H-11,

HO–), 3.95 (dt, J = 3.8 and 10.7 Hz, H-8), 5.61 (d, J = 4.8 Hz, H-6), 6.23 (d, J = 9.8 Hz, H-1) and 6.78 (d, J = 9.8 Hz, H-2); ^{13}C NMR (Table 1).

Table 2 ^{13}C NMR data of elemanolides (2), (3), (12)–(15) (50.3 MHz, $CDCl_3$, δ values)

	(2)	(3)	(12)	(13)	(15)[b]
C_1	148.1	147.9	148.1	148.4	147.7
C_2	111.2	111.3	111.1	111.1	111.2
C_3	112.9	113.9	113.7	112.8	113.9
C_4	146.0	145.3	145.4	146.0	145.2
C_5	48.9[a]	52.6[a]	52.8[a]	49.5	52.9[a]
C_6	30.1	27.7	29.2	29.6	27.1
C_7	40.2[a]	49.4[a]	52.1[a]	43.7[a]	56.6[a]
C_8	76.1	79.7	79.4	76.7	77.1
C_9	40.1	42.8	42.3	39.9	42.3
C_{10}	39.3	41.9	41.9	38.6	41.9
C_{11}	141.1	139.3	41.4	42.5[a]	49.3
C_{12}	170.5	170.7	179.3	–	176.6
C_{13}	120.8	117.5	12.5	14.3	22.5
C_{14}	19.2	18.9	18.8	18.7	18.8
C_{15}	24.4	24.7	24.5	24.5	24.7

[a] Chemical shifts are interchangeable

[b] Aromatic carbons for compound (15): 124.3, 129.0, 129.6 and 138.1

Methyl 8α-Hydroxy-3-oxo-7αH,11βH-eudesma-1,4-dien-12-oate (5b)

Activated Zn dust (1.20 g) and 0.2 mL of AcOH were added to a solution of lactone (4) containing 558 mg (1.9 mmol) in 9 mL anhydrous MeOH. After refluxing for 15 min, the reaction mixture was cooled to room temperature, filtered to remove the Zn and diluted with 60 mL of MeOH. Then, 0.6 mL of concentrated H_2SO_4 was added and the mixture was heated under reflux for 2 h. After *in vacuo* evaporation of part of the MeOH, the mixture was diluted with water and 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. The (1:1) hexane-EtOAc eluted compound (5b) (459 mg, 77%), with the following features: m.p. 93–94°C (hexane-EtOAc); IR ν_{max}: 3450–3300, 3040, 3000–2850, 1725, 1660, 1630, 1610, 1200, 1180, 1060, 835 cm^{-1}; ^1H NMR δ: 1.17 (s, H-14), 1.21 (d, J = 7.0 Hz, H-13), 1.60 (dddd, J = 2.3, 3.8, 10.8 and 13.9 Hz, H-7), 1.85 (s, H-15), 2.04 (dd, J = 4.5 and 12.5 Hz, H-9β), 2.13 (t, J = 14.0 Hz, H-6β), 2.5–2.6 (broad signal, HO–), 2.76 (dd, J = 3.8 and 14.0 Hz, H-6α), 2.92 (dq, J = 2.3 and 7.0 Hz, H-11), 3.66 (s, $-COOCH_3$), 3.99 (dt, J = 4.5 and 10.8 Hz, H-8), 6.14 (d, J = 9.8 Hz, H-1) and 6.65 (d, J = 9.8 Hz, H-2); ^{13}C NMR (Table 1).

3-Oxo-5,7-11αH,4,8βH-eudesman-8,12-olide (8a) and *3-oxo-4,7,11,αH,5,8βH-eudesman-8,12-olide* (8b)
An amount of 714 mg (2.57 mmol) of hydroxyester (5b) in 21 mL of acetone was hydrogenated over a 5% (175 mg) Pd/C catalyst. After stirring at room temperature for 12 h, the hydrogenation mixture was filtered and concentrated *in vacuo*. A solution of the oily residue and *p*-toluenesulphonic acid (in a catalytic amount) in 63 mL of dry benzene was heated under reflux for 90 min. After *in vacuo* evaporation of the solvent, the reaction product was chromatographed on silica gel with various CH_2Cl_2–isobutyl alcohol mixtures in ratios of 100:0, 100:0.1, 100:0.2 and 100:0.3, yielding (8a) (283 mg, 44%) and (8b) (182 mg, 28%). Compound (8a) had the following features: m.p. 189–190°C (hexane–CH_2Cl_2); high-resolution MS: 250.1576 (M^+, 29.9%); $C_{13}H_{22}O_3$ required 250.1569 and further peaks at 235 (3.3%), 206 (13.7%) and 191 (8.4%); IR ν_{max} : 3000–2880, 1770, 1700, 1460, 1220, 1000 cm^{-1}; ^1H NMR δ: 0.99 (d, J = 6.6 Hz, H-15), 1.16 (d, J = 7.4 Hz, H-13), 1.1–1.4 (m, overlapped signals, H-5 and 2 H-6), 1.18 (s, H-14), 1.38 (t, J = 11.7, H-9α), 1.63 (dt, J = 5.0 and 13.6 Hz, H-1α), 1.82 (ddd, J = 2.0, 6.5 and 13.6 Hz, H-1β), 2.12 (dd, J = 3.8 and 11.7 Hz, H-9β), 2.28 (dq, J = 6.6 and 11.6 Hz, H-4), 2.35 (ddd, J = 2.0, 5.0 and 14.2 Hz, H-2α), 2.49 (dd, J = 6.5 and 14.2 Hz, H-2β), 2.65 (quint., J = 7.4 Hz, H-11) and 4.28 (dt, J = 3.8 and 11.5 Hz, H-8); ^{13}C NMR (Table 1). Compound (8b) had the following features: m.p. 99–100°C (hexane–CH_2Cl_2); high resolution MS: 250.1581 (M^+, 26.4%), $C_{15}H_{22}O_3$ required 250.1569 and further peaks at 235 (0.9%), 206 (19.7%) and 191 (20.6%); IR ν_{max}: 2980–2860, 1770, 1710, 1470, 1215, 1185 and 1000 cm^{-1}; ^1H NMR δ: 1.0 (d, J = 6.5 Hz, H-15), 1.12 (s, H-14), 1.18 (d, J = 7.5 Hz, H-13), 1.5–2.0 (m, overlapped signals, 2 H-1 and 2 H-6), 1.83 (dd, J = 4.2 and 11.5 Hz, H-9β), 2.14 (t, J = 11.5 Hz, H-9α), 2.22 (dt, J = 3.8 and 14.0 Hz, H-2β), 2.55 (dq, J = 6.5 and 12.4 Hz, H-4), 2.65 (m, J = 6.5 Hz, H-11) and 4.38 (dt, J = 4.2 and 11.5 Hz, H-8); ^{13}C NMR (Table 1).

3-Oxo-5,7,αH,4,8,11βH-eudesman-8,12-olide (8c)
A solution of 57 mg (2.3 mmol) of (8a) in 1.2 mL of THF was treated at –78°C for 15 min with a solution of lithium diisopropylamide prepared from 0.42 mL (3 mmol) of diisopropylamine in 2.3 mL of THF, and a 1.6 M solution(1.8 mL, 2.9 mmol) of n-BuLi in hexane. The temperature was raised to 0°C and the reaction mixture was stirred for 2 h. Addition of an aqueous solution of NH_4Cl and application of the usual procedure yielded 52 mg (91%) of compound (8c), with the following physico-chemical features: m.p. 185–186°C (hexane-CH_2Cl_2; high resolution MS: 250.1578 (M^+, 18.7%), $C_{15}H_{22}O_3$ required 250.1569 and further peaks at 235 (3.1%), 206 (15.6%) and 191 (7.0%); IR ν_{max}: 2990–2870, 1770, 1710, 1450, 1190, 1120 and 1005 cm^{-1}; ^1H NMR δ: 1.01 (d, J = 6.6 Hz, H-15), 1.19 (s, H-14), 1.20 (d, J = 7.2 Hz, H-13), 1.1–1.5 (m, overlapped signals, H-5, 2 H-6), 1.34 (t, J = 11.8 Hz, H-9α), 1.85 (ddd, J = 2.0, 6.7 and 12.0 Hz, H-1β), 2.10 (dd, J = 3.8 and 11.8 Hz, H-9β), 2.2–2.3 (m, overlapped signals, H-2, H-4β), 2.38 (ddd, J = 2.0, 5.3 and 14.0 Hz, H-2α), 2.51 (dd, J = 6.7 and 14.0 Hz, H-2β), 2.55 (dq, J = 7.2 and 14.0 Hz, H-11) and 4.03 (dt, J = 3.8 and 11.8 Hz, H-8); ^{13}C NMR (Table 1).

5,7αH,4,8,11βH-Eudesm-2-en-8,12-olide (9)
A solution containing 573 mg (2.29 mmol) of compound (8a) in 6 mL of benzene plus 540 mg (2.5 mmol) of *p*-toluenesulphonylhydrazine and two drops of $BF_3 \cdot OEt_2$ was stirred at room temperature for 3 h. The mixture was then diluted with CH_2Cl_2, dried and concentrated *in vacuo*. The crude tosylhydrazone, dissolved in 11.5 mL of THF, was treated at –78°C for 15 min with a lithium diisopropylamide solution prepared from 4.2 mL (30 mmol) of diisopropylamine in 22.5 mL of THF and a 1.6 M solution (18 mL, 28.8

mmol) of n-BuLi in hexane. The temperature was raised to 0°C and the reaction mixture was stirred for 2 h. By the usual procedure was obtained an oil which was chromatographed on silica gel; an 85:15 hexane-ether mixture eluted from the column 189 mg (35%) of compound (9), with the following physical and spectral features: m.p. 95–96°C (hexane–CH_2Cl_2); high resolution MS: 234.1629 (M^+, 43%), $C_{15}H_{22}O_2$ required 234.1620 and further peaks at 219 (100%), 193 (15%), 175 (7.8%) and 149 (23.1%); IR ν_{max}: 3000, 2990–2800, 1750, 1645, 1135, 1000, 720 and 680 cm^{-1}; ^1H NMR δ: 0.93 (s, H-15), 0.9–1.2 (m, overlapped signals, 2 H-6 and H-5), 1.00 (d, J = 6.7 Hz, H-15), 1.21 (d, J = 7.0 Hz, H-13), 1.35 (t, J = 11.5 Hz, H-9α), 1.3–1.5 (m, partially overlapped with H-9α, H-7), 1.7–2.1 (m, overlapped signals, 2 H-2 and H-4), 2.03 (dd, J = 3.5 and 11.5 Hz, H-9β), 2.27 (dq, J = 3.5 and 7.0, H-11), 3.97 (ddd, J = 3.5, 11.5 and 13.0 Hz, H-8), 5.6–5.4 (m, H-2 and H-3); ^{13}C NMR (Table 1).

2,3-Dihydroxy-5,7αH,4,8,11βH-eleman-8,12-olide (10)

A solution containing 225 mg (0.96 mmol) of olefin (9) in 80 mL of 1:1 MeOH–CH_2Cl_2 at –78°C was treated with a stream of ozone (*ca.* 5 mmol/h) for 20 min. Then, 196 mg (4.47 mmol) of $NaBH_4$ at –78°C was added. At 15-min intervals for a further 45 min was added an identical amount of sodium borohydride, also at –78°C. The reaction mixture was warmed to 0°C and stirred for 1 h. By the usual procedure and chromatography with EtOAc was obtained 176 mg (68%) compound (10), with the following features: m.p. 115–116°C (ether); high resolution MS: 270.1816 (M^+, 7.6%), $C_{15}H_{26}O_4$ required 270.1824 and further peaks at 252 (16.1%), 225 (14.2%), 222 (26.3%), IR ν_{max}: 3350–3150, 2990–2860, 1770, 1040 and 1000 cm^{-1}; ^1H NMR δ 0.78 (d, J = 6.9 Hz, H-15), 0.98 (s, H-14), 1.19 (d, J = 6.8 Hz, H-13), 2.27 (dq, J = 6.8 and 12.2 Hz, H-11), 2.2–2.4 (broad signal overlapped with H-11, 2 HO–), 3.33 (t, J = 10.4 Hz, H-3), 3.43 (dd, J = 3.4 and 10.4 Hz, H-3'), 3.6–3.8 (m, partially overlapped with H-8, 2 H-2), 3.89 (dt, J = 4.3 and 10.8 Hz, H-8). ^{13}C NMR (Table 1).

2,3-Di-o-nitrophenylseleno-5,7αH,4,8,11,βH-eleman-8,12-olide (11)

An amount of 175 mg (0.65 mmol) of diol (10) was treated with 710 mg (3.15 mmol) of *o*-nitrophenylselenocyanate in 6 mL of THF and 0.8 mL (3.25 mmol) of n-Bu_3P at room temperature for 6 h. After precipitation and solvent removal, the residue was chromatographed on silica gel, from which a 1:1 mixture of hexane and ether eluted 385 mg (93%) of (11), a yellow product with the following features: m.p. 140–142°C (hexane-acetone); IR ν_{max}: 2990–2860, 1770, 1590, 1570, 1510, 1340, 1010 and 735 cm^{-1}; ^1H NMR δ 1.02 (s, H-14), 1.04 (d, J = 7.8 Hz, H-15), 1.22 (d, J = 7.0 Hz, H-13), 2.3 (dq, J = 7.0 and 12.0 Hz, H-11), 2.6–3.1 (m, overlapped signals, 2 H-2 and 2 H-3), 3.89 (t, J = 10.0 Hz, H-8), 7.1–7.5 (m, overlapped signals, aromatic H in *meta-* and *para-* to $-NO_2$), 8.11 (d, J = 8.0 Hz, aromatic H in *ortho-* to $-NO_2$), 8.22 (d, J = 8.0 Hz, aromatic H in *ortho-* to $-NO_2$). ^{13}C NMR (Table 1).

5,7αH,8,11βH-Elema-1,3-dien-8,12-olide (12)

To a solution containing 77 mg (0.12 mmol) of (11) in 1 mL of THF was added 0.065 mL (1.13 mmol) of 30% aqueous hydrogen peroxide at 0°C. The product was treated by the usual procedure and chromatographed on silica gel, from which a 9:1 hexane-ether mixture eluted 15 mg (53%) of compound (12), with the following features: m.p. 92–93°C (hexane); high resolution MS: 234.1640 (M^+, 5.6%), $C_{15}H_{22}O_2$ required 234.1620 and further peaks at 219 (2.6%), 190 (1.4%), 175 (0.3%) and 161 (4.6%); IR ν_{max}: 3060, 2990–2840, 1770, 1640, 1100, 990, 920 and 900 cm^{-1}; ^1H NMR δ 1.05 (s, H-14), 1.18 (d, J = 6.9 Hz, H-13),

1.5–1.9 (m, overlapped signals 2 H-6, H-7 and H-9α), 1.69 (s, signals overlapped with the last multiplet, H-15), 1.95 (dd, J = 3.9 and 12.0 Hz, H-9β), 2.09 (dd, J = 3.3 and 11.3 Hz, H-5), 2.31 (dq, J = 6.9 and 12.0 Hz, H-11), 3.98 (ddd, J = 3.9, 10.0 and 12.0 Hz, H-8), 4.61 (broad s, H-3), 4.89 (broad s, H-3'), 4.93 (d, J = 17.2 Hz, H-2), 4.96 (d, J = 10.9 Hz, H-2'), 5.83 (dd, J = 10.9 and 17.2 Hz, H-1); ^{13}C NMR (Table 2).

5,7,8αH,11βH-Elema-1,3-dien-8,12-olide (13)

An amount of 9.5 mg (0.04 mmol) of compound (12) was refluxed for 1.5 h in a mixture of 2.4 mL of 96% aqueous ethanol and 0.12 mL of 1 M aqueous NaOH. The solvent was then removed *in vacuo* and residual water was eliminated by repeated azeotroping with benzene. The residual salt was suspended in 2 mL of THF, cooled to 0°C and treated with 0.09 mL (0.61 mmol) of triethylamine, followed by 36 μL (0.46 mmol) of methanesulphonyl chloride. After 1 h, 0.3 mL of a 0.25 M NaOH solution was added and the mixture was warmed at 50°C for 1.5 h. After acidification with 1.5 mL of 5% HCl, the usual procedure and preparative TLC with 85:15 hexane–EtOAc yielded 3.3 mg (35%) of product (12) and 3.0 mg (32%) of its epimer (13), the latter of which had the following features: high resolution MS: 234. 1636 (M$^+$, 3.0%), $C_{15}H_{22}O_2$ required 234.1620 and further peaks at 219 (5.8%), 190 (0.5%), 175 (1.0%) and 161 (20.3%); IR ν_{max}: 3080, 3000–2850, 1770 and 1640 cm^{-1}; ^{1}H NMR δ 1.09 (s, H-13), 1.28 (d, J = 7.5 Hz, H-14), 1.52 (s, H-15), 1.63 (t, J = 12.0 Hz, H-9α), 1.97 (dd, J = 4.0 and 12.0 Hz, H-9β), 2.0–2.2 (m overlapped with H-9β, H-7), 2.38 (dq, J = 1.9 and 7.5 Hz, H-11), 4.50 (broad s, H-3), 4.67 (q, J = 4.0 Hz, H-8), 4.90 (broad s, H-3'), 4.93 (d, J = 17.0 Hz, H-2), 4.95 (d, J = 10.0 Hz, H-2') and 5.76 (dd, J = 10.0 and 17.0 Hz, H-1); ^{13}C NMR (Table 2).

11β-Phenylseleno-5,7αH,8βH-elema-1,3-dien-8,12-olide (15)

To a THF solution of lithium diisopropylamide prepared from 0.061 mL (0.43 mmol) of diisopropylamine, 1.6 M n-BuLi in hexane (0.27 mL, 0.43 mmol), and 0.7 mL of dry THF at –78°C was added dropwise 48 mg (0.21 mmol) of compound (12) in 0.7 mL of dry THF. After stirring at –78°C for 1 h, 87 mg (0.45 mmol) of phenylselenyl chloride in 1.5 mL of dry THF and 70 μL of HMPT was added dropwise at –78°C. The mixture was stirred at the same temperature for 40 min, then warmed to –40°C and kept at this temperature for 40 min. The reaction was quenched by adding 1.5 mL of 0.6 M aqueous HCl. The product was treated as usual and chromatographed on silica gel, from which an 85:15 hexane-ether mixture eluted 41 mg (50%) of compound (15) and 9 mg (17%) of compound (12). The former had the following features: m.p. 140–142°C (ether-hexane); IR ν_{max}: 3080, 2890, 1770, 1640, 1130, 1015, 920, 760 and 700 cm^{-1}; ^{1}H NMR δ 1.75–1.85 (m overlapped signals, 2 H-6 and H-7), 1.97 (dd, J = 3.8 and 11.9 Hz, H-9β), 2.12 (dd, J = 4.6 and 10.0 Hz, H-5), 4.46 (ddd, J = 3.8, 9.8 and 11.9 Hz, H-8), 4.67 (broad s, H-3), 4.92 (broad s, H-3'), 4.94 (d, J = 17.3 Hz, H-2), 4.96 (d, J = 10.9 Hz, H-2'), 5.82 (dd, J = 10.9 and 17.3 Hz, H-1), 7.2–7.5 (m, aromatic H in *meta-* and *para-*), 7.62 (dd, J = 1.5 and 7.0 Hz, aromatic H in *ortho-*); ^{13}C NMR (Table 2).

5,7αH,8βH-Elema-1,3,11(13)trien-8,12-olide (3)

To a solution containing 13.5 mg (0.039 mmol) of compound (15) in 0.4 mL of THF cooled to 0°C was added 10 μL (0.096 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 6.8 mg (85%) of compound (3), with the following features: high resolution MS: 232.1448 (M$^+$, 3.1%), $C_{15}H_{20}O_2$ required 232.1458 and further peaks at 217 (8.3%) and 204 (2.9%); IR ν_{max}: 3080, 3000–2860, 1770, 1640, 1140, 1000, 920 and 820 cm^{-1}; ^{1} NMR δ 1.07 (s, H-14), 1.72 (t, overlapped with H-9β, J = 13.0 Hz, H-6β), 1.73 (s, H-15), 1.76 (t, J = 11.8 Hz, H-9β),

1.98 (dd, overlapped with H-6α, J = 3.7 and 11.8 Hz, H-9α), 2.00 (dt, J = 3.5 and 13.0 Hz, H-6α), 2.15 (dd, J = 3.5 and 12.5 Hz, H-5), 2.46 (qt, J = 3.0 and 11.8 Hz, H-7), 3.95 (dt, J = 3.7 and 11.8 Hz, H-8), 4.63 (broad s, H-3), 4.90 (broad s, H-3'), 4.95 (d, J = 17.6 Hz, H-2), 4.97 (d, J = 10.9 Hz, H-2'), 5.39 (d, J = 3 Hz, H-13), 5.84 (dd, J = 10.9 and 17.6 Hz, H-1) and 6.06 (d, J = 3 Hz, H-13'); ^{13}C NMR (Table 2).

11β-Phenylseleno-5,7,8αH-elema-1,3-dien-8,12-olide (16) and *5,7,8αH-elema-1,3,11(13)-trien-8,12,-olide* (2) An amount of 25 mg (0.064 mmol) of compound (15) was refluxed in a mixture of 3.6 mL of 96% aqueous ethanol and 0.18 mL of 1M aqueous NaOH for 1 h, 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 3 mL of THF, cooled to 0°C and treated with 0.15 mL (1.02 mmol) of triethylamine, followed by 72 μL (0.91 mmol) of methanesulphonyl chloride. After 3 h, 1.5 mL of a 0.25 M NaOH solution was added and the mixture was warmed at 50°C for 3 h. After acidification with 3 mL of 5% HCl, the usual procedure and preparative TLC with 85:15 hexane-EtOAc yielded 7.5 mg (30%) of starting product (15), 3.5 mg (13%) of its epimer (16) and 5 mg (33%) of compound (2). The latter compound had the following spectral features: high resolution MS: 232.1446 (M^+, 2.5%), $C_{15}H_{20}O_2$ required 232.1458 and further peaks at 217 (7.2%) and 204 (2.5%); IR ν_{max}: 3080, 3000–2850, 1765, 1640, 1165, 1125, 940, 920 and 820 cm^{-1}; ^1H NMR δ 1.02 (s, H-14), 1.69 (s, H-15), 1.5–2.0 (m overlapped signals, 2 H-6 and 2 H-9), 2.03 (dd, J = 3.5 and 12.3 Hz, H-5), 3.02 (dt, J = 5.9 and 10.5 Hz, H-7), 4.55 (t overlapped with H-3, J = 5.9 Hz, H-8), 4.59 (broad s, H-3), 4.84 (broad s, H-3'), 4.96 (d, J = 10.5 Hz, H-2), 4.97 (d, J = 17.6 Hz, H-2'), 5.56 (broad s, H-13), 5.79 (dd, J = 10.5 and 17.6 Hz, H-1) and 6.16 (broad s, H-13').

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