Tetrahedron Vol. 40, No. 24, pp. 5243 to 5248, 1984
Printed in the U.S.A.

0040-4020/84 $3.00 + .00

TOTAL SYNTHESES OF (+)-TEMISIN, (+)-MELITENSIN AND RELATED ELEMANOLIDES FROM (−)-ARTEMISIN[1]

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(*Received in UK 3 January* 1984)

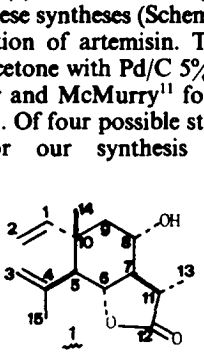
Abstract—(+)-Temisin, (+)-melitensin, and related sesquiterpene lactones have been synthesized from (−)-artemisin.

The elemanolides (+)-temisin (**1**), (+)-melitensin (**2**) and 11 (13)-dehydromelitensin (**3**) first were isolated from *Artemisia cina*,[2] *Centaurea melitensis*[3] and *Centaurea pullata*[4] respectively, and recently **2** and **3** have been isolated in this department[5] from *Centaurea aspera* ssp. *stenophylla*. The total synthesis of (±)-temisin have been reported,[6] however, the synthesis of the (+)-isomer has not been achieved.

In this paper we describe the syntheses of (+)-temisin, (+)-melitensin and 11,13-dehydromelitensin from (−)-artemisin (**7**). As the total synthesis of (−)-artemisin has been accomplished,[7,8] the syntheses of **1**, **2** and **3** reported in this paper are formal total syntheses of these compounds. The dehydrotemisin **4** has also been synthesized because of the cytotoxic and antitumor activities[9] of some sesquiterpenes having the α-methylene-γ-lactone unit. Finally, we have opened a route to 8β-hydroxyelemanolides,[10] in which 8-epitemisin (**5**) and 8-epimelitensin (**6**) have been synthesized. (−)-Artemisin was chosen as the starting material because it possesses the same absolute configuration at C6, 7, 8, 10, 11 as that of temisin and melitensin.

Syntheses of temisin (**1**) *and melitensin* (**2**)

The first step of these syntheses (Scheme 1) was the catalytic hydrogenation of artemisin. This reaction was carried out in acetone with Pd/C 5% as catalyst, according to Cocker and McMurry[11] for the hydrogenation of santonin. Of four possible stereoisomers, the right one for our synthesis is the γ-tetrahydroartemisin,[12] which was isolated as its *t*-butyldimethylsilyl ether after treatment of the crude tetrahydroartemisin with *t*-butyldimethylsilyl chloride in DMF/imidazole.[13] This treatment has three aims: (1) it protects the free OH at C_8 during the subsequent process; (2) the relatively strong basic property of imidazole epimerizes the C_4-Me of tetrahydroartemisins; and (3) it facilitates the chromatographic separation of stereoisomers. So by chromatography on silica gel we separated as the main product the *t*-butyldimethylsilyl ether **8b**, as is shown in the ^{1}H NMR by the triplet at δ 3.90 (J = 10.6 Hz) for H–6, which means that the protons H–5 and H–7 are *trans*-diaxial; moreover, it gives the γ-tetrahydroartemisin[12] by cleavage of the silyl ether. The next step was the formation of a $\Delta^{2,3}$ double bond through a Shapiro reaction.[14] Thus the ketolactone **8b**, transformed into the corresponding tosylhydrazone, was treated in THF at − 78° with lithium diisopropylamide, affording the olefin **9**, as shown by IR(3020, 1610 cm^{-1}) and ^{1}H NMR (δ 5.4 for 2H). The olefin **9**, treated at − 78° with ozone (sat. sol. in CH_2Cl_2) followed by reduction ($NaBH_4$), furnished the diol **10**: IR, 3560–3200 cm^{-1} and ^{1}H NMR spectrum, overlapped signals at δ 3.4–4.4 for 6H, 2C$\underline{H_2}$OH, H–6 and H–8. The next stage was the formation of two vinyl groups, carried out in two steps through the di-*o*-nitrophenylselenide **11**. This was prepared by treating the diol **10** with *o*-nitrophenylselenocyanate and tri-n-butylphosphine in THF according to Grieco's method;[15] the di-*o*-nitrophenylselenide (**11**)



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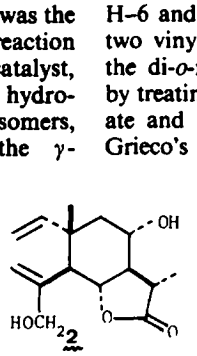

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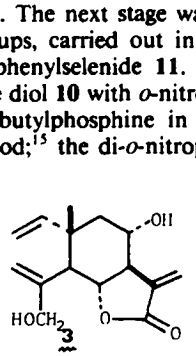

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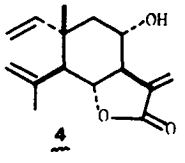

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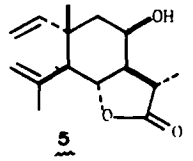

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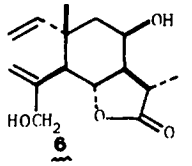

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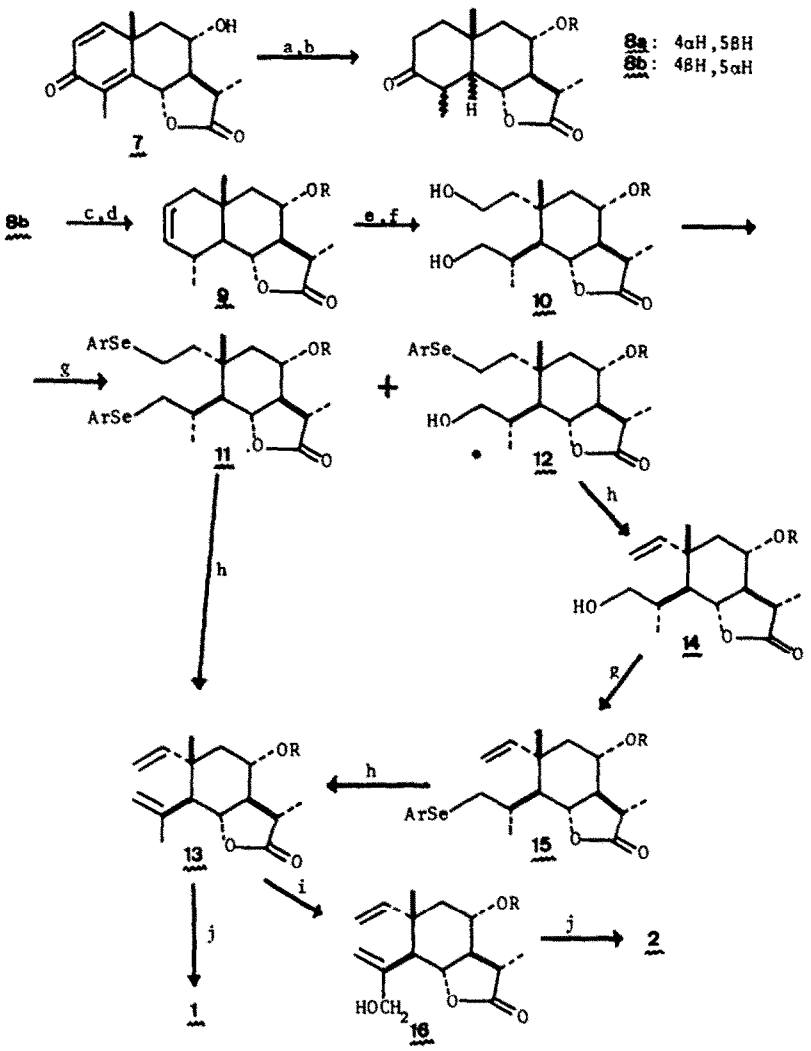


Scheme 1. a, H_2, Pd/C; b, TBDMSCl, imidazole; c, $TsNHNH_2$, $BF_3 \cdot Et_2O$; d, LDA; e, O_3; f, $NaBH_4$; g, ArSeCN, Bu_3P; h, 50% H_2O_2; i, SeO_2, 80% *t*-BuOOH; j, n-Bu_4NF R = TBDMS-; Ar = *o*-$NO_2C_6H_4$-.

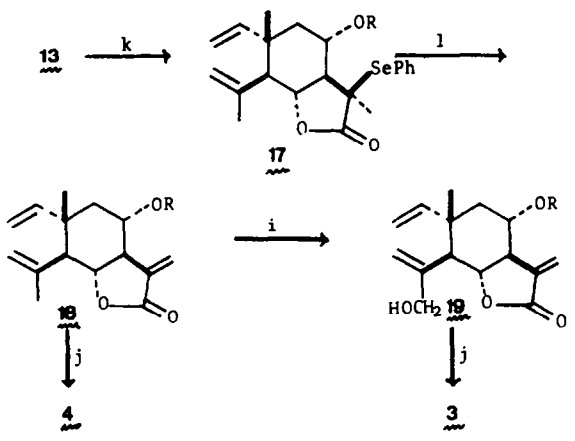
was always accompanied by a minor amount of monoselenide (**12**). Oxidation of **11** with 50% of hydrogen peroxide followed by spontaneous elimination of *o*-nitrophenylselenenic acid afforded the crystalline compound **13**. In agreement with this structure the IR (970, 910 and 890 cm^{-1}) and the ^1H NMR spectra showed typical bands for vinyl groups. In the parallel way the monoselenide **12** was transformed into the olefinic alcohol **14**, which was converted into the corresponding selenide **15**. Upon oxidation, **15** yielded the divinyl compound **13**. The allylic oxidation of C_4-Me of **13** was carried out with SeO_2/*t*-BuOOH at room temperature.[16] Compound **16** was obtained in 50% yield and 46% of starting product was recovered.[17] The structure of **16** was fully supported by the IR (3520, 1755, 1640 cm^{-1}) and the ^1H NMR spectra (δ 3.98, 2H, br. s. partially overlapped with H-6 and H-8, $-C\underline{H}_2-OH$).

Cleavage of silyl ether **13** with n-Bu_4NF led to (+)-temisin (**1**), m.p. 227–228°, which was identical with natural temisin (NMR).[6]

Similar cleavage of the silyl ether **16** gave (+)-melitensin (**2**), m.p. 180–183°, identical with natural melitensin (NMR and IR).[3]

Syntheses of dehydromelitensin (**3**) *and dehydrotemisin* (**4**)

The introduction of the exomethylene group in the α-position of the γ-lactone ring (Scheme 2) was carried out by phenylselenenylation[18] of **13** (PhSeCl/LDA) to give the α-phenylselenolactone **17**. Structure **17** showed a singlet in the NMR spectrum at δ 1.62 ppm (C_{11}-Me, overlapped with C_4-Me). Oxidative *syn*-elimination of **17** with 30% H_2O_2 afforded **18**. This structure was supported by the IR (1770 cm^{-1}) and ^1H NMR spectra (signals at δ 5.89 and 6.15 ppm, 1H each, dd, $=CH_2$). Allylic oxidation of **18** at C_{15} (SeO_2/*t*-BuOOH) gave the silyl ether **19**. Cleavage of **19** afforded 11(13)-dehydromelitensin (**3**), an oil, which was identical with natural 11(13)-dehydromelitensin (NMR and IR).[4] In a similar way cleavage of the silyl ether (**18**) afforded 11(13)-dehydrotemisin (**4**). This structure was supported by the



Scheme 2. i, SeO_2, 80% *t*-BuOOH; k, LDA, PhSeCl; l, 30% H_2O_2.

IR (3460 and 1745 cm^{-1}) and ^1H NMR spectra (δ 4.7–5.8, 3H, vinyl pattern; 5.95 and 6.13 ppm, 1H each, d, $=CH_2$).

Syntheses of 8-*epitemisin* (**5**) *and* 8-*epimelitensin* (**6**)

The starting material for these syntheses (Scheme 3) is temisin (**1**), which was oxidized by Collins reagent to the 8-oxo-derivative (**20**) (IR : 1780 and 1730 cm^{-1}). Reduction of **20** with LiAlH (O-t-Bu)$_3$ in THF at 0° afforded 9-epitemisin (**5**), as indicated by the coupling constants of H_8 (double triplet, J = 3.0 and 2.6 Hz). Allylic oxidation of 8-epitemisin (**5**) gave 8-epimelitensin (**6**).

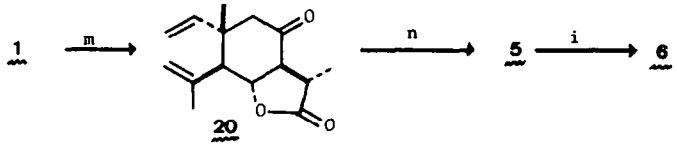
EXPERIMENTAL

M.ps were determined in capillary tubes with a Buchi melting point apparatus, and are uncorrected. IR spectra were recorded on a Perkin–Elmer 281 spectrometer. ^1H NMR spectra were determined with Perkin–Elmer R12B (60 MHz) and Varian H-100 (100 MHz) spectrometers, using TMS as internal standard. Mass spectra were performed at 70 eV on a Varian 156 machine, using the direct inlet system. Optical rotations were determined on a Perkin–Elmer 141 polarimeter.

3-*Oxo*-8α-*t*-*butyldimethylsilyloxy*-4,6,11β,5,7α*H*-*eudesman*-6,12-*olide* (**8b**). Artemisin (**7**) (1.80 g, 6.87 mmol) in acetone (48 mL) was hydrogenated (35 min) using Pd/C 5% (0.42 g) as catalyst. The hydrogenated mixture, in DMF (50 mL), was treated with *t*-butyldimethylsilyl chloride (3.65 g, 24 mmol) and imidazole (4.67 g, 68 mmol). The temperature of the reaction was raised to 30–40°, with stirring over 3.5 h. The reaction product, extracted with ethyl acetate, was chromatographed on silica gel, from which hexane:ether (7:3) eluted two compounds. The first was **8a** (0.625 g, 24%), an oil. IR: ν_{max} 3000–2840, 1780 (γ-lactone), 1710 (ketone), 1470, 1450, 1400, 1360, 1345, 1250, 1110, 1070, 1005, 985, 865, 835 and 775 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz), δ 4.32 (dd, 1H, J = 4.0 and 11.3 Hz, H–6), 3.96 (dt, 1H, J = 4.6 and 10.0 Hz, H–8), 1.35 (d, 3H, J = 6.6 Hz, C_{11}–Me), 1.15 (s, 3H, C_{10}–Me), 1.14 (d, 3H, J = 6.0 Hz, C_4–Me), 0.90 (s, 9H, $SiCMe_3$) and 0.10 (s, 6H, $SiMe_2$). This oil crystallized very slowly from hexane–ether, m.p. 105°. The second eluted product was **8b** (1.444 g, 55%), m.p. 176–178° (ethanol); IR: ν_{max} (KBr) 3000–2850, 1775 (γ-lactone), 1705 (ketone), 1470, 1455, 1400, 1375, 1340, 1255, 1215, 1115, 1085, 995, 965, 860 and 830 cm^{-1}. ^1H NMR ($CDCl_3$, 60 MHz), δ 3.98 (dt, 1H, J = 4.3 and 10.0 Hz, H–8 overlapped with H–6), 3.90 (t, 1H, J = 10.6 Hz, H–6), 1.35 (d, 3H, J = 6.6 Hz, C_{11}–Me), 1.25 (d, 3H, J = 7.3 Hz, C_4–Me), 1.19 (s, 3H, C_{10}–Me), 0.90 (s, 9H, $SiCMe_3$) and 0.10 (s, 6H, $SiMe_2$). Compounds (**8a**) and (**8b**) on cleavage of the silyl group with Bu_4NF in THF gave δ-tetrahydroartemisin m.p. 213–215° $[\alpha]_D^{25}$ + 46.7° (c 0.028, EtOH) and γ-tetrahydroartemisin, m.p. 227–229°, $[\alpha]_D^{25}$ + 50° (c 0.5, EtOH) respectively, in good agreement with the literature.[12]

8α-*t*-*Butyldimethylsilyloxy*-4,6,11β*H*,5,7α*H*-*eudesm*-2-*en*-6,12-*olide* (**9**) *from* (**8b**). A solution of **8b** (0.294 g, 0.77 mmol) in benzene (1.9 mL), with *p*-toluenesulphonylhydrazine (0.176 g, 0.95 mmol) and a drop of $BF_3.Et_2O$ was stirred 3 h at 30°. The mixture was diluted with CH_2Cl_2 (7.5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude tosylhydrazone, dissolved in THF (4 mL), was treated at −78° (15 min) with lithium diisopropylamide [prepared from di-isopropylamine (1.0 g, 9.9 mmol) in THF (7.5 mL) and a 1.6 M solution (6.1 mL, 9.76 mmol) of n-BuLi in hexane]. The temperature was raised to 0° and the reaction was stirred 2 h. Usual work up gave an oil, which was chromatographed on silica gel; hexane:ether (95:5) eluted from the column compound **9** (0.142 g, 50%), m.p. 127–128° (hexane–ether); high res. MS: 307.1722 (M^+–C_4H_9), $C_{17}H_{27}O_3Si$ requires 307.1729; IR: ν_{max} (KBr) 3020, 2970–2840, 1770 (γ-lactone), 1610, 1470, 1440, 1380, 1255, 1210, 1115, 1075, 995, 960, 870, 835, 770, 690 and 660 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 5.60–5.40 (br, s, 2H, H–2 and H–3), 3.81 (dt, 1H, J = 4.6 and 10.0 Hz, H–8, partially overlapped with H–6), 3.69 (t, 1H, J = 10.6 Hz, H–6), 1.30 (d, 3H, J = 7.3, C_{11}–Me), 1.22 (d, 3H, J = 6.6 Hz, C_4–Me), 0.94 (s, 3H, C_{10}–Me), 0.90 (s, 9H, $SiCMe_3$) and 0.10 (s, 6H, $SiMe_2$).

8α-*t*-*Butyldimethylsilyloxy*-2,3-*dihydroxy*-5,7α*H*,6,11β*H*-*eleman*-6,12-*olide* (**10**). The olefin **9** (0.407 g, 1.11 mmol) in ethanol (49 mL) at −78° was treated with a precooled



Scheme 3. i, SeO_2, 80% *t*-BuOOH; m, CrO_3·py; n, LiAlH(O-*t*-Bu)$_3$.

(−78°) sat. solution of ozone in CH_2Cl_2 (49 mL, *ca.* 1.20 mmol of ozone). After 15 min, 0.049 g (1.29 mmol) $NaBH_4$ was added at −78°. At 15 min intervals for an additional 45 min an equal amount of sodium borohydride was added (−78°). The reaction mixture was warmed to room temp. and the solvent was removed *in vacuo*. The usual work up afforded **10** (0.386 g, 87%), m.p. 151–152°(ethyl acetate); high res. MS: 325.1844 ($M^+ - C_4H_9 - H_2O$), $C_{17}H_{29}O_4Si$ requires 325.1835; IR: ν_{max} (KBr) 3560–3200, 2990, 2860, 1775 (γ-lactone), 1480, 1445, 1390, 1260, 1200, 1115, 1085, 1015, 980, 945, 865, 840 and 775 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 4.40–3.40 (m, 4H, H-2, H-6, H-8), 3.55 (d, 2H, J = 8.0 Hz, H-3), 3.40–2.90 (br. signal, 2H, 2OH), 2.60–2.10 (m, 1H, H-11), 1.34 (d, 3H, J = 7.0 Hz, C_{11}-Me), 0.98 (s, 3H, C_{10}-Me), 0.92 (d, overlap, 3H, C_4-Me), 0.89 (s, 9H, $SiCMe_3$) and 0.09 (s, 6H, $SiMe_2$).

8α-t-Butyldimethylsilyloxy-2,3-di-o-nitrophenylseleno-5,7αH,6,11βH-eleman-6,12-olide (**11**). The diol **10** (0.375 g, 0.94 mmol) was treated with *o*-nitrophenyl selenocyanate (1.020 g, 4.49 mmol) in THF (7.8 mL) and n-Bu_3P (0.906 g, 4.49 mmol) over 6 h at room temperature and under Ar. After solvent removal the residue was chromatographed on silica gel, from which hexane:ether (1:1) eluted two yellow products. The first was **11** (0.569 g, 79%); IR: ν_{max} 3080–3060, 2950–2840, 1775 (γ-lactone), 1590, 1565, 1510, 1470–1450, 1390, 1330, 1305, 1250, 1125, 1090, 1000, 950, 860, 850, 840, 770 and 725 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 8.35–8.00 (m, 2H, aromatic H *o*-NO_2) 7.60–7.00 (m, 6H, aromatic H *m*- and *p*-NO_2), 4.20–3.60 (m, 1H, H-8), 4.10 (t, 1H, J = 11.0 Hz, H-6), 3.05 (d, 2H, J = 7.0 Hz, H-3), 3.20–2.70 (m, 2H, H-2), 1.36 (d, J = 6.6 Hz, 3H, C_{11}-Me), 1.25 (d part, overlap with C_{10}-Me, 3H, C_4-Me), 1.04 (s, 3H, C_{10}-Me), 0.90 (s, 9H, $SiCMe_3$) and 0.12 (s, 6H, $SiMe_2$). The second eluted product was **12** (0.072 g, 13%) m.p. 112–115° (hexane–ether); IR: ν_{max} (KBr) 3600–3200, 3060, 2980–2860, 1770 (γ-lactone), 1590, 1565, 1510, 1470–1450, 1390, 1330, 1305, 1250, 1135, 1090, 1035, 995, 960, 860, 835, 775 and 730 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 8.25 (d, 1H, J = 8.0 Hz, aromatic H *o*-NO_2), 7.65–7.20 (m, 3H, aromatic H *m*- and *p*-NO_2), 4.30–3.80 (m, 2H, H-6 and H-8), 3.55 (d, 2H, J = 7.3 Hz, H-3), 3.0 (m, 2H, H-2), 1.34 (d, 3H, J = 6.6 Hz, C_{11}-Me), 1.04 (s, 3H, C_{10}-Me), 1.00 (d part. overlap, 3H, C_4-Me), 0.92 (s, 9H, $SiCMe_3$), and 0.12 (s, 6H, $SiMe_2$).

8α-t-Butyldimethylsilyloxy-5,7αH,6,11βH-elema-1,3-dien-6,12-olide (**13**) *from* (**11**). Compound **11** (0.57 g, 0.74 mmol) in THF (7 mL) was treated at 0° with 50% aqueous hydrogen peroxide (0.4 mL, 5.8 mmol). After addition was complete, the reaction was left at room temp. for 3.5 h. The product was worked up in the usual way and chromatographed on silica gel, from which hexane:ether (9:1) eluted compound **13** (0.23 g, 85%), m.p. 174–175° (hexane–ether); high res. MS: 307.1719 ($M^+ - C_4H_9$), $C_{17}H_{27}O_3Si$ requires 307.1729; IR: ν_{max} (KBr) 3080, 2980-2860, 1780 (γ-lactone), 1640, 1470, 1375, 1255, 1210, 1140, 1070, 1005, 970, 910, 890, 870, 830 and 770 cm^{-1}. ^1H NMR ($CDCl_3$, 60 MHz) δ 5.77 (dd, 1H, J = 9.6 and 17.0 Hz, H-1), 5.10–4.75 (m, 2H, H-2), 5.05 and 4.70 (two br.s., 2H, H-3), 4.12 (t, 1H, J = 11.6 Hz, H-6), 4.30–3.70 (m, 1H, H-8), 2.25 (d, 1H, J = 11.6 Hz, H-5), 1.78 (s, 3H, C_4-Me), 1.35 (d, 3H, J = 7.5 Hz, C_{11}-Me), 1.10 (s, 3H, C_{10}-Me), 0.90 (s, 9H, $SiCMe_3$) and 0.09 (s, 6H, $SiMe_2$).

8α-t-Butyldimethylsilyloxy-3-hydroxy-5,7αH,6,11βH-elem-1-en-6,12-olide (**14**). Treatment of **12** (0.47 g, 0.80 mmol) with 50% H_2O_2 (0.44 mL, 6.31 mmol) by the method mentioned above afforded **14** (0.26 g, 85%), an oil; IR: ν_{max} 3580–3280, 3090, 2980–2860, 1775 (γ-lactone), 1640, 1470–1465, 1410, 1385, 1255, 1210, 1130, 1085, 1035, 1025, 995, 950, 910, 865, 840 and 775 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 5.71 (dd, 1H, J = 10.0 and 17.6 Hz, H-1) 5.20–4.85 (m, 2H, H-2), 3.94 (m, 2H, H-6 and H-8) 3.36 (d, 2H, J = 6.6 Hz, H-3) 2.41 (br., 1H, OH), 2.60–2.00 (m, 1H, H-11), 1.30 (d, 3H, J = 6.6 Hz, C_{11}-Me), 1.11 (s, 3H, C_{10}-Me), 1.07 (d overlap with C_{10}-Me, 3H, C_4-Me), 0.91 (s, 9H, $SiCMe_3$) and 0.10 (s, 6H, $SiMe_2$).

8α-t-Butyldimethylsilyloxy-3-o-nitrophenylseleno-5,7αH,6,11βH-elem-1-en-6,12-olide (**15**). The product **14** (0.106 g, 0.28 mmol) was treated with *o*-nitrophenyl selenocyanate (0.251 g, 1.11 mmol) in THF (2.3 mL) and tri-n-butylphosphine (0.223 g, 1.11 mmol) as above. It was obtained **15** (0.098 g, 62%), a waxy product; IR: ν_{max} 3090, 2960, 2860, 1770, 1635, 1590, 1565, 1510, 1460, 1410, 1385, 1330, 1255, 1130, 1085, 995, 950, 915, 860, 830, 775 and 725 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 8.30–8.10 (m, 1H, aromatic H *o*-NO_2), 7.60–7.0 (m, 3H, aromatic H *m*- and *p*-NO_2) 5.70 (dd, 1H, J = 9.6 and 17.3 Hz, H-1), 5.10–4.70 (m, 2H, H-2), 4.20–3.60 (m, 2H, H-6 and H-8), 2.95 (d, 1H, J = 7.3 Hz, H-3), 2.60–2.0 (m, 1H, H-11). 1.31 (d, 3H, J = 7.3, C_{11}-Me), 1.08 (d overlap with C_{10}-Me, 3H, C_4-Me), 1.05 (s, 3H, C_{10}-Me), 0.87 (s, 9H, $SiCMe_3$), and 0.06 (s, 6H, $SiMe_2$).

8α-t-Butyldimethylsilyloxy-5,7αH,6,11βH-elema-1,3-dien-6,12-olide (**13**) *from* (**15**). Compound **15** (0.254 g, 0.45 mmol) in THF (3.7 mL) was treated as above with 50% H_2O_2 (0.1 mL, 1.44 mmol), providing **13** (0.111 g, 66%).

(+)-Temisin (**1**). The product **13** (0.150 g, 0.412 mmol) in THF (2.7 mL) was treated with n-$Bu_4NF.3H_2O$ (0.51 g, 1.63 mmol, dried overnight *in vacuo* over P_2O_5), stirring the mixture at room temperature for 1h. The cleavage product was worked up in the usual way and chromatographed on silica gel, from which ethyl acetate eluted **1** (0.103 g, 100%) as a white crystalline product, m.p. 227–228°, $[\alpha]_D^{20} + 63°$ (c 0.028, EtOH); high res. MS: 250.1576 (M^+), $C_{15}H_{22}O_3$ requires 250.1569; IR: ν_{max} (KBr) 3500–3400, 3070, 2990–2840, 1755 (1770 in $CHCl_3$), 1640, 1460, 1430, 1380, 1360, 1140, 985, 965, 905 and 890 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz), δ 5.80 (dd, 1H, J = 10.9 and 17.0 Hz, H-1), 5.05 (s, 1H, H-3), 5.01 (dd, 1H, J = 10.9 and 1.0 Hz, H-2), 4.95 (dd, 1H, J = 17.0 and 1.0 Hz, H-2′), 4.70 (s, 1H, H-3′), 4.12 (dd, 1H, J = 10.6 and 11.9 Hz, H-6), 3.95 (dt, 1H, J = 4.7 and 10.0 Hz, H-8), 2.65 (dq, 1H, J = 7.0 and 12.0 Hz, H-11), 2.26 (d, 1H, J = 11.9 Hz, H-5), 1.77 (s, 3H, C_4-Me), 1.39 (d, 3H, J = 7.0 Hz, C_{11}-Me) and 1.09 (s, 3H, C_{10}-Me).

8α-t-Butyldimethylsilyloxy-15-hydroxy-5,7αH, 6,11βH-elema-1,3-dien-6,12-olide (**16**). A mixture of 0.012 g of sublimed SeO_2 in CH_2Cl_2 (0.17 mL) and 50 μL of 80% *t*-BuOOH was stirred over 30 min. To this reagent the product **13** (0.084 g, 0.23 mmol) was added slowly with good stirring for 3 h at room temp. The reaction was stopped by addition of benzene and the product was worked up in the usual way and chromatographed on silica gel, from which hexane–ether eluted successively two products: the starting compound (0.038 g, 46%) and **16** (0.043 g, 50%) m.p. 180–181° (hexane–ether); high res. MS: 323.1671 ($M^+ - C_4H_9$), $C_{17}H_{27}O_4Si$ requires 323.1678; IR: ν_{max} (KBr), 3520, 3080, 2980–2860, 1755 (γ-lactone), 1640, 1470–1460, 1410, 1380, 1360, 1250, 1215, 1135, 1075, 1035, 990, 905, 870, 835 and 770 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 5.83 (dd, 1H, J = 9.6 and 17.3 Hz, H-1), 5.34 (s, 1H, H-3), 4.98 (d, 1H, J = 9.6 Hz, H-2), 4.91 (d, 1H, J = 17.6 Hz, H-2′), 4.90 (s, 1H, H-3′), 4.14 (dd, overlap with H-8 and H-15, 1H, J = 11.3 and 12.0 Hz, H-6), 3.98 (b.s. overlap with H-6, and H-8, 2H, H-15), 3.91 (dt, 1H, J = 5.3 and 10.0 Hz, H-8), 2.50 (m, 1H, H-11), 2.35 (d, 1H, J = 12.0 Hz, H-5), 1.34 (d, 3H, J = 6.6 Hz, C_{11}-Me), 1.09 (s, 3H, C_{10}-Me), 0.90 (s, 9H, $SiCMe_3$) and 0.10 (s, 6H, $SiMe_2$).

(+)-Melitensin (**2**). The product **16** (0.088 g, 0.231 mmol) in THF (1.7 mL) was treated with n-$Bu_4NF.3H_2O$ (0.32 g, 1.03 mmol) as above, providing **2** (0.055 g, 89%) m.p. 180–183° (hexane–ethyl acetate); $[\alpha]_D^{20} + 60°$ (c 0.028, EtOH); high res. MS: 266.1517 (M^+), $C_{15}H_{22}O_4$ requires 266.1518; IR: ν_{max} (KBr), 3600–3400, 3090, 3000–2960, 1755 (1775 in $CHCl_3$), 1635, 1450, 1410, 1380, 1360, 1140, 1050, 1000, 980, 965 and 910 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 5.78 (dd, 1H, J = 10.7 and 17.3 Hz, H-1), 5.39 (s, 1H, H-3), 5.03 (dd, 1H, J = 10.7 and 1.0 Hz, H-2), 4.97 (dd, 1H,

J = 17.3 and 1.0 Hz, H-2'), 4.95 (s, 1H, H-3'), 4.15 (dd partly overlap with H-8 and H-15, 1H, J = 10.7 and 11.3 Hz, H-6), 4.03 (s, 2H, H-15), 3.98 (dt partly overlap with H-15, 1H, J = 4.6 and 10.4, H-8) 2.54 (dq, 1H, J = 7.0 and 11.0 Hz, H-11), 2.40 (d, 1H, J = 11.3 Hz, H-5), 1.56 (s, 2H, 2OH), 1.39 (d, 3H, J = 7.0 Hz, C_{11}-Me) and 1.10 (s, 3H, C_{10}-Me).

8α-t-Butyldimethylsilyloxy-11β-phenylseleno-5,7αH,6βH-elema-1,3-dien-6,12-olide (**17**). To a dry THF solution of lithium diisopropylamide, from diisopropylamine (0.13 mL, 0.94 mmol), 1.6M BuLi (0.59 mL, 0.94 mmol) and dry THF (1.5 mL), at −78°, was added dropwise 0.176 g (0.48 mmol) of (**13**) in dry THF (1.5 mL). After stirring at −78° for 1 h phenylselenide chloride (0.186 g, 0.97 mmol) in dry THF (3 mL) and HMPT (0.15 mL) was added dropwise at −78°. The mixture was stirred at −78° for 40 min, then warmed to −40° and kept at that temperature for 40 min. The reaction was quenched by addition of 0.6 M HCl aq. (3 mL). The product was worked up in the usual way and chromatographed on silica gel, from which hexane–ether eluted two compounds: The first was **17** (0.155 g, 61%), an oil; IR ν_{max} 3080, 2980–2860, 1775, 1640, 1565, 1485, 1460, 1440, 1410, 1395, 1380, 1365, 1280, 1260, 1200, 1120, 1030, 1000, 910, 885, 865, 800, 760 and 710 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz), δ 7.75–7.50 and 7.45–7.20 (m, 5H, H aromatics), 5.75 (dd, 1H, J = 9.6 and 17.6 Hz, H-1), 5.01 (s, 1H, H-3), 5.10–4.70 (m overlap with H-3, 2H, H-2), 4.50 (s, 1H, H-3'), 4.50–4.00 (m overlap with H-6, 1H, H-8) 4.20 (t, 1H, J = 11.6 Hz, H-6), 2.10 (d, 1H, J = 11.6 Hz, H-5) 2.00 (t partly overlap with C_4-Me and C_{11}-Me, 1H, J = 11.6 Hz, H-7) 1.62 (s, 6H, C_4-Me and C_{11}-Me), 1.00 (s, 3H, C_{10}-Me), 0.92 (s, 9H, $SiCMe_3$), 0.26 (s, 3H, SiMe) and 0.15 (s, 3H, SiMe). The second eluted compound was starting material **13** (0.031 g, 17%).

8α-t-Butyldimethylsilyloxy-5,7αH,6βH-elema-1,3,11-trien-6,12-olide (**18**). To compound **17** (0.111 g, 0.21 mmol) in THF (2 mL) cooled to 0° was added 30% H_2O_2 (50 mL, 0.58 mmol). The mixture was stirred for 1 h at room temp., then poured into brine and extracted with EtOAc. The extract was dried and concentrated *in vacuo*. The oily residue was purified by preparative tlc (silica gel PF_{254}, hexane:ether 1:1) to give **18** (0.065 g, 84%), m.p. 85–86° (hexane–CH_2Cl_2); high res. MS: 305.1575 ($M^+-C_4H_9$), $C_{17}H_{25}O_3Si$ requires 305.1573; IR: ν_{max} (KBr), 3080, 2980–2860, 1770, 1670, 1640, 1460, 1400, 1380, 1360, 1255, 1135, 1080, 1000, 975, 940, 910, 895, 860, 835 and 775 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 6.15 (dd, 1H, J = 1.3 and 3.0 Hz, H-13), 5.89 (dd, 1H, J = 1.3 and 3.0 Hz, H-13'), 5.85 (dd overlap with H-13', 1H, J = 9.6 and 17.3 Hz, H-1), 5.08 (s, overlap with H-2, 1H, H-3), 5.10–4.80 (m, 2H, H-2), 4.73 (s, 1H, H-3'), 4.10 (dd overlap with H-8, 1H, J = 10.6 and 12.0 Hz, H-6), 4.02 (m, 1H, H-8), 2.63 (tt, 1H, J = 3.0 and 10.6 Hz, H-7), 2.37 (d, 1H, J = 12.0 Hz, H-5), 1.78 (d, 3H, J = 1.3 Hz, C_4-Me), 1.08 (s, 3H, C_{10}-Me), 0.90 (s, 9H, $SiCMe_3$) and 0.12 (s, 6H, $SiMe_2$).

8α-t-Butyldimethylsilyloxy-15-hydroxy-5,7αH,6βH-elema-1,3,11-trien-6,12-olide (**19**). To a mixture of sublimed SeO_2 (0.033 g) in CH_2Cl_2 (0.5 mL) and 0.13 mL of 80% *t*-BuOOH, was added **18** (0.025 g, 0.07 mmol) and the mixture was treated as above. There was obtained starting product (0.011 g, 44%) and **19** (0.004 g, 15%), m.p. 58–60° (hexane–CH_2Cl_2); high res. MS: 321.1531 ($M^+-C_4H_9$), $C_{17}H_{25}O_4Si$ requires 321.1522; IR: ν_{max} (KBr), 3560–3200, 3090, 3000–2860, 1765, 1665, 1645, 1460, 1410, 1255, 1135, 1080, 1045, 990, 935, 910, 860, 835 and 770 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 6.17 (d, 1H, J = 3.0 Hz, H-13), 5.90 (d, 1H, J = 3.0 Hz, H-13'), 5.83 (dd partly overlap with H-13', 1H, J = 9.6 and 18.3 Hz, H-1), 5.42 (s, 1H, H-3), 5.05 (d, 1H, J = 9.6 Hz, H-2), 4.97 (d overlap with H-3, 1H, J = 18.3 Hz, H-2'), 4.96 (s, 1H, H-3'), 4.19 (t overlap with H-8 and H-15, 1H, J = 11.3 Hz, H-6), 4.05 (s, 2H, H-15), 4.30–3.90 (m, 1H, H-8), 2.68 (m partly overlap with H-5, 1H, H-7), 2.48 (d, 1H, J = 11.6 Hz, H-5), 1.90–1.50 (m overlap. with OH, 2H, H-9), 1.11 (s, 3H, C_{10}-Me), 0.92 (s, 9H, $SiCMe_3$) and 0.14 (s, 6H, $SiMe_2$).

Dehydromelitensin (**3**). The product **19** (0.009 g, 0.023 mmol) dissolved in THF (0.3 mL) was treated with n-$Bu_4NF.3H_2O$ (0.036 g, 0.11 mmol) as above, providing **3** (0.005 g, 82%), an oil; high res. MS: 246.1248 (M^+-H_2O), $C_{15}H_{18}O_3$ requires 246.1256; IR: ν_{max} 3580–3150, 3090, 2980, 2860, 1760, 1640, 1405, 1130, 1050, 970 and 910 cm^{-1}. ^1H NMR ($CDCl_3$, 60 MHz), δ 6.12 (d, 1H, J = 3.0 Hz, H-13), 5.94 (d partly overlap with H-1, 1H, J = 3.0 Hz, H-13'), 5.77 (dd, 1H, J = 10.0 and 18.0 Hz, H-1), 5.36 (s, 1H, H-3), 5.00 (d, 1H, J = 10.0 Hz, H-2), 4.93 (d overlap with H-3', 1H, J = 18.0 Hz, H-2'), 4.91 (s, 1H, H-3'), 4.11 (t partly overlap with H-8 and H-15, 1H, J = 12.0 Hz, H-6), 4.01 (s, 2H, H-15) 4.40–3.90 (m, 1H, H-8), 2.48 (d, 1H, J = 12.0 Hz, H-5), 1.81 (s, 2H, 2 OH) and 1.08 (s, 3H, C_{10}-Me).

Dehydrotemisin (**4**). The product **18** (0.039 g, 0.11 mmol) dissolved in THF (0.8 mL) was treated with n-$Bu_4NF.3H_2O$ (0.148 g, 0.47 mmol) as above, giving **4** (0.014 g, 53%), m.p. 144–145° (hexane–CH_2Cl_2); high res. MS: 248.1408 (M^+), $C_{15}H_{20}O_3$ requires 248.1412; IR: ν_{max} (KBr), 3460, 3080, 2980–2860, 1745, 1640, 1400, 1380, 1360, 1065, 965 and 900 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz), δ 6.13 (d, 1H, J = 3.0 Hz, H-13), 5.95 (d partly overlap with H-1, 1H, J = 3.0 Hz, H-13'), 5.82 (dd, 1H, J = 11.0 and 16.0 Hz, H-1), 5.06 (s overlap with H-2, 1H, H-3), 5.05 (dd, 1H, J = 1.5 and 11.0 Hz, H-2), 4.90 (dd, 1H, J = 1.5 and 16.0 Hz, H-2') 4.69 (s, 1H, H-3'), 4.09 (t partly overlap with H-8, 1H, J = 11.5 Hz, H-6), 4.30–3.70 (m, 1H, H-8), 2.34 (d 1H, J = 11.5 Hz, H-5), 1.78 (s, 3H, C_4-Me) and 1.08 (s, 3H, C_{10}-Me).

8-Oxo-5,7αH,6,11βH-elema-1,3-dien-6,12-olide (**20**). CrO_3 (0.318 g, 3.18 mmol) was added into a mixture of CH_2Cl_2 (4.0 mL) and pyridine (0.65 mL, 6.38 mmol) at 0° and stirred for 15 min. Compound **1** (0.040 g, 0.16 mmol) in CH_2Cl_2 (3 mL) was added and the mixture was stirred at 0° for 4 h. The mixture was diluted with CH_2Cl_2 and filtered through celite. The filtrate was worked up in the usual way and separated by preparative tlc. Two products were obtained: starting material (0.005 g, 12%) and **20** (0.027 g, 68%), m.p. 114–116° (hexane–CH_2Cl_2); high res. MS: 248.1401 (M^+), $C_{15}H_{20}O_3$ requires 248.1413; IR: ν_{max} (KBr), 3090, 3010, 3000–2860, 1780, 1730, 1650, 1640, 1455, 1410, 1380, 1240, 975, 910 and 890 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz), δ 5.93 (dd, 1H, J = 10.6 and 17.0 Hz, H-1), 5.16 (s overlap with H-2, 1H, H-3), 5.10 (dd, 1H J = 10.6 and 1.0 Hz, H-2), 4.97 (dd, 1H, J = 17.0 and 1.0 Hz, H-2'), 4.81 (s, 1H, H-3'), 4.28 (t, 1H, J = 11.6 Hz, H-6), 2.73 (d overlap with H-5, 1H, J = 14.0 Hz, H-9), 2.16 (d, 1H, J = 14.0 Hz, H-9'), 1.84 (d, 3H, J = 1.0 Hz, C_4-Me), 1.30 (d, 3H, J = 6.6 Hz, C_{11}-Me) and 1.10 (s, 3H, C_{10}-Me).

8-Epitemisin (**5**). Compound **20** (0.022 g, 0.088 mmol) in THF (2 mL) was treated at 0° with LiAlH(O-t-Bu)$_3$ (0.068 g, 0.27 mmol) with good stirring for two hours. The product was worked up in the usual way. Two products were separated by preparative tlc: temisin **1** (0.003 g, 4%) and 8-epitemisin **5** (0.018 g, 81%), m.p. 161–162° (hexane–CH_2Cl_2); high res. MS: 250.1576 (M^+), $C_{15}H_{22}O_3$ requires 250.1569; IR: ν_{max} (KBr), 3540–3390, 3090, 3080, 2990, 2880, 1750, 1640, 1455, 1415, 1380, 1130, 1000, 970, 920 and 890 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz), δ 5.84 (dd, 1H, J = 10.0 and 17.3 Hz, H-1), 4.70–5.15 (m partly overlap with H-6 4H, H-2 and H-3) 4.53 (t, 1H, J = 11.6 Hz, H-6), 4.31 (dt, 1H, J = 2.6 and 3.0 Hz H-8), 2.76 (dq, 1H, J = 7.0 and 12.3 Hz, H-11), 2.31 (d, 1H, J = 11.6 Hz, H-5), 1.83 (d, 3H, J = 1.0 Hz, C_4-Me), 1.27 (s, 3H, C_{10}-Me) and 1.23 (d, 3H, J = 7.0 Hz, C_{13}-Me).

8-Epimelitensin (**6**). To sublimed SeO_2 0.014 g in CH_2Cl_2 (0.2 mL) and 80% *t*-BuOOH (60 μL), 8-epitemisin **5** (0.013 g, 0.052 mmol) was added as above. There were isolated **5** (0.003 g, 23%) and **6** (0.009 g, 57%), m.p. 115–116° (hexane–ether); high res. MS: 248.1418 ($M^+ -H_2O$), $C_{15}H_{20}O_3$ requires 248.1412; IR: ν_{max} (KBr) 3500–3300, 3090,

3000–2860, 1750, 1635, 1460, 1450, 1410, 1380, 1260, 1220, 1190, 1135, 1055, 1000, 970, 910, 890 and 835 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz), δ 5.83 (dd, 1H, J = 9.0 and 17.0 Hz, H–1), 5.41 (s, 1H, H–3), 5.11 (s overlap with H–2, 1H, H–3'), 5.20–4.70 (m overlap with H–6, 2H, H–2), 4.55 (t, 1H, J = 12.0 Hz, H–6), 4.50–4.20 (m, 1H, H–8), 4.08 (s, 2H, H–15), 3.0–2.50 (m overlap with H–5, 1H, H–11), 2.48 (d, 1H, J = 12.0 Hz, H–5), 1.80 (s, 2H, 2 OH), 1.30 (s, 3H, C_{10}–Me) and 1.26 (d, 3H, J = 6.0 Hz, C_{11}–Me).

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