Tetrahedron. Vol 33, pp. 2785 to 2789. Pergamon Press 1977 Printed in Great Britain

STUDIES IN THE SYNTHESES OF SESQUITERPENE LACTONES—II

CHEMICAL TRANSFORMATION OF α-SANTONIN INTO REYNOSIN, SANTAMARINE, EPOXYSANTAMARINE AND 1β-HYDROXYARBUSCULIN A

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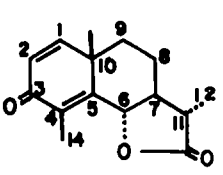
(*Received in Japan* 28 *March* 1977; *Received in UK for publication* 31 *May* 1977)

Abstract—Eudesmane type α-methylene-γ-lactones, reynosin (1), santamarine (2), epoxysantamarine (3) and 1β-hydroxyarbusculin A (4) have been synthesized from α-santonin.

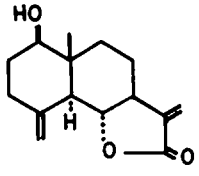
The α-methylene-γ-lactone unit has been assigned a central role in the mechanism of action of the many cytotoxic and antitumor agents which bear this functional group. In this paper we wish to report the chemical transformation of α-santonin into eudesmane type α-methylene-γ-lactones, reynosin (**1**),[1,2] santamarine (**2**),[3] epoxysantamarine (**3**)[1,3] and 1β-hydroxyarbusculin A (**4**),[2] which contain a β(eq)-OH group at the C_1-position and another functional group at the C_4-position. Since decalin derivatives with an equatrial OH group at the C_1-position are known to undergo solvolytic rearrangement into hydroazulene derivatives,[4,5] it is expected that these compounds or the methodologies in these syntheses are useful for the syntheses of certain cytotoxic guaianolides and pseudoguaianolides[6] which also contain an α-methylene-γ-lactone group.

Synthesis of reynosin.[7] The starting material of this synthesis is the ketal (**5**) which was prepared in 15.4% overall yield from α-santonin by the method reported.[8] Treatment of **5** with bromine gave a dienone (**7**) by spontaneous dehydrobromination and deketalization in 62.7% yield as a crystalline material. In agreement with the structure **7** the product exhibited the UV (MeOH) absorption at 268 nm and the IR ($CHCl_3$) absorption at 1670 cm^{-1}. The NMR spectrum in $CDCl_3$ showed peaks at δ 5.56 and 5.83 (m, each, $\prec^{H}_{H}$), 5.87 (broad d, J = 10.0 Hz, C_2-H) and 7.08 (dd, J = 0.8, 10.0 Hz, C_3-H) ppm. Alternatively the dienone (**7**) was obtained in the following manner. Epoxidation of **5** gave **6** in quantitative yield. Treatment of **6** with aqueous acetic acid gave 36.1% yield of **7** accompanied with 30.3% yield of vulgarin (**11**). Reduction of **7** gave an exomethylene ketone (**8**) in 68.5% yield. In agreement with the structure **8** the product exhibited an IR ($CHCl_3$) absorption at 1703 cm^{-1} and NMR ($CDCl_3$) peaks at δ 5.10 and 5.22 (m, $\prec^{H}_{H}$) ppm. The exomethylene ketone (**8**) was reduced to give an alcohol (**9**). Phenylselenenylation of **9**[9] afforded an α-phenylseleno lactone (**10**) in 30.8% overall yield from **8**. The NMR spectrum of this compound showed a singlet at δ 1.53 ppm assigned to C_{11}-Me. Oxidative syn-elimination[9,10] of **10** with 30% H_2O_2 gave reynosin (**1**) in a quantitative yield, m.p. 145° (lit.[1] 145–146°), which was identical with natural reynosin[1,2] in NMR ($CDCl_3$)[11] and IR ($CHCl_3$) spectra.

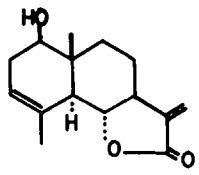
Synthesis of santamarine and epoxysantamarine.[7] The starting materials for this synthesis are vulgarin (**11**) and the C_4-epimer of vulgarin (**12**).[8] Compounds **11** and **12** were converted to the βγ-unsaturated ketone (**13**)[12] in



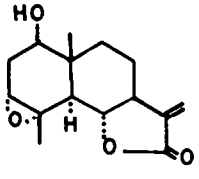
α-Santonin



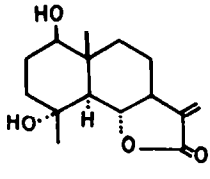
Reynosin (**1**)



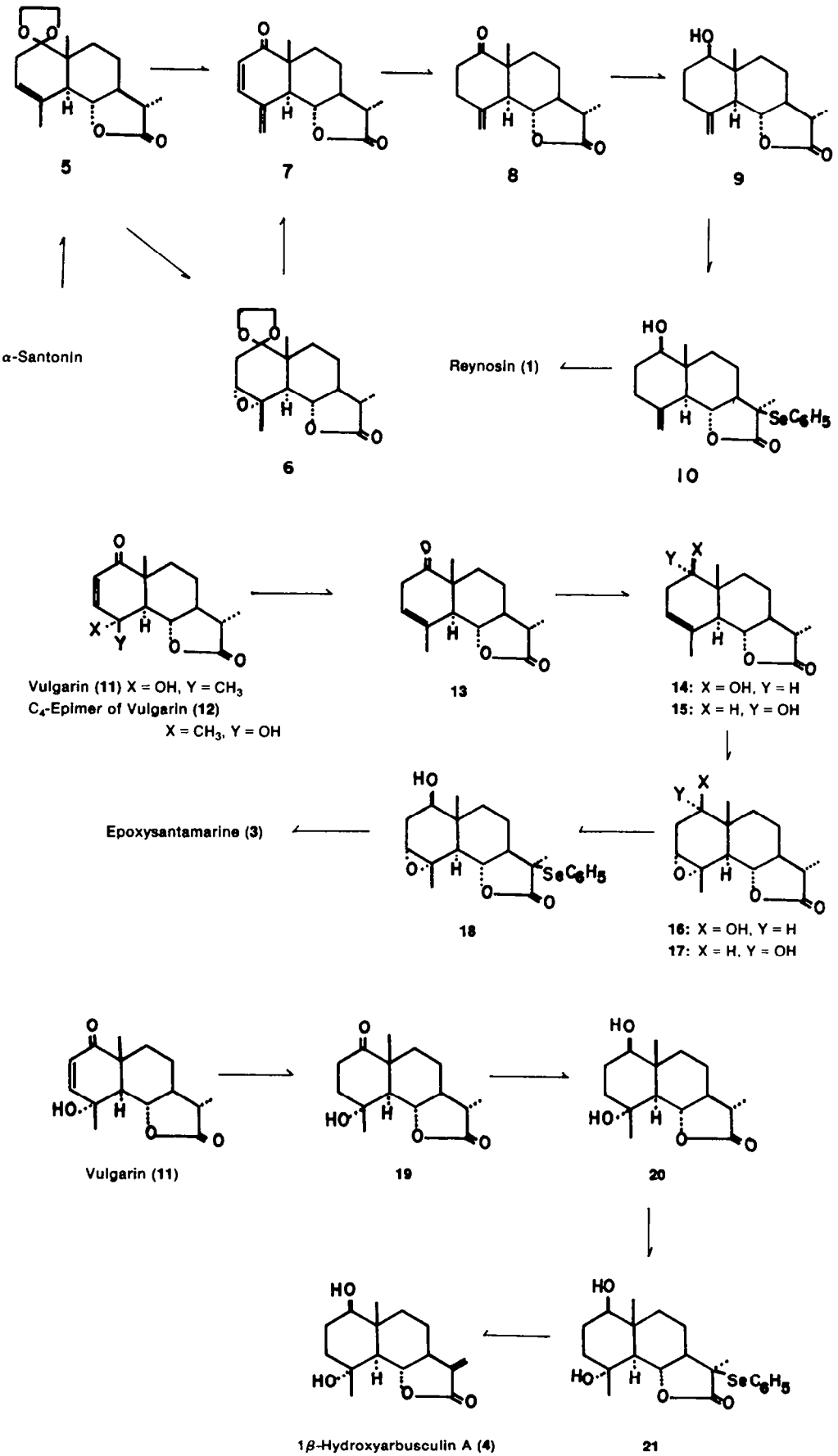
Santamarine (**2**)



Epoxysantamarine (**3**)



1β-Hydroxyarbusculin A (**4**)


5
7
8
9
α-Santonin
6
Reynosin (1)
10
Vulgarin (11) X = OH, Y = CH3
C4-Epimer of Vulgarin (12)
X = CH3, Y = OH
13
14: X = OH, Y = H
15: X = H, Y = OH
Epoxysantamarine (3)
18
16: X = OH, Y = H
17: X = H, Y = OH
Vulgarin (11)
19
20
1β-Hydroxyarbusculin A (4)
21

76.7% and 70.6% yields respectively. The position of the double bond in **13** was assigned by the NMR spectrum which showed a broadened singlet at δ 1.98 (C_4–Me) ppm and a broadened multiplet at δ 5.57 ($W_{h/2}$ = 9.0 Hz, C_3–H) ppm. Reduction of **13** gave a 5:1 mixture of epimeric alcohols (**14**[3] and **15**). β-Equatrial configuration of the OH group at C_1 in **14** was deduced from the NMR spectrum which showed a signal at δ 3.63 (dd, J = 7.0, 10.0 Hz, C_1–H) ppm. Conversion of **14** to santamarine (**2**) has already been established.[13] Epoxidation of **14** and **15** gave the corresponding **16** and **17** in 67.2% and 12.6% overall yield respectively. In agreement with the structure **16** the NMR spectrum showed peaks at δ 1.46 (s, C_4–Me), 3.01 (dd, J = 0.8, 3.3 Hz, C_3–H) and 3.43 (dd, J = 6.5, 10.0 Hz, C_1–H) ppm. Phenylselenenylation of **16**[9] gave α-phenylseleno lactone (**18**) in 85.4% yield. In agreement with the structure **18** the NMR spectrum showed a singlet at δ 1.55 ppm assigned to C_{11}–Me. Oxidative syn-elimination of **18** gave epoxysantamarine in 85.8% yield, m.p. 243–248° (dec.) (lit.[1] 243.5–246°), which was identical with natural epoxysantamarine[1,3] in NMR spectrum.

Synthesis of 1β-*hydroxyarbusculin A.*[7] Catalytic hydrogenation of vulgarin (**11**) gave dihydrovulgarin (**19**).[12] Reduction of **19** gave a diol (**20**). Phenylselenenylation of **20** afforded an α-phenylseleno lactone (**21**) in 51.6% overall yield. In agreement with the structure **21** the NMR spectrum of this compound showed a singlet at δ 1.56 ppm assigned to C_{11}–Me. Oxidative syn-elimination of **21** gave 1β-hydroxyarbusculin A in 86.8% yield, m.p. 194–196° (lit.[2] 194–196°), which was identical with natural 1β-hydroxyarbusculin A[2] in NMR ($CDCl_3$) and IR ($CHCl_3$) spectra.

As the total synthesis of α-santonin has been accomplished,[14] the syntheses of reynosin (**1**), santamarine (**2**), epoxysantamarine (**3**) and 1β-hydroxyarbusculin A (**4**) reported in this paper are the formal total syntheses of these compounds.

EXPERIMENTAL

All m.ps were uncorrected. IR spectra were recorded on a Shimadzu IRG-I spectrometer. NMR spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$ containing TMS as an internal standard unless otherwise stated. Mass spectra were recorded on a Hitachi RMU-6D spectrometer.

1,1 - *Ethylenedioxy* - 5αH,6,11βH - *eudesm* - 3 - *en* - 6,13 - *olide* (**5**) was prepared in 15.4% overall yield from α-santonin.[8] This material showed the following data, m.p. 130–131°; $\nu_{max}^{CHCl_3}$ 1765, 892, 863, 852 cm^{-1}; δ 1.03 (s, C_{10}–Me), 1.22 (d, J = 6.5 Hz, C_{11}–Me), 1.85 (broad s, C_4–Me), 3.5–4.2 ($\left[\begin{matrix}O\\O\end{matrix}\right>$ and C_6–H), 5.29 (m, $W_{h/2}$ = 7.0 Hz, C_3–H). (Found: C, 69.70; H, 8.27. $C_{17}H_{24}O_4$ requires: C, 69.83; H, 8.27%).

1 - *Oxo* - 5αH,6,11βH - *eudesm* - 2,4(14) - *dien* - 6,13 - *olide* (**7**) *from* **5**. Into a soln of **5** (72 mg, 0.246 mmol) in $CHCl_3$ (3 ml) was added Br_2 (47 mg, 0.294 mmol) in $CHCl_3$ (1 ml). The soln was stirred at 0° for 30 min and poured into sat NaCl aq (10 ml). The mixture was extracted with $CHCl_3$. The extract was washed with $NaHCO_3$ aq and sat NaCl aq, dried (Na_2SO_4) and concentrated *in vacuo*. The residue showed three spots (R_f 0.62, 0.58 and 0.53) on TLC [silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1:9)] and was purified by TLC in the same condition. The third band (R_f 0.53) gave 38 mg (62.7%) of **7** as a crystalline material; $\nu_{max}^{CHCl_3}$ 1670 cm^{-1}; λ_{max}^{MeOH} 268 nm; δ 1.07 (s, C_{10}–Me), 1.24 (d, J = 6.7 Hz, C_{11}–Me), 2.83 (dt, J = 10.0, 1.8 Hz, C_5–H), 4.21 (t, J = 10.0 Hz, C_6–H) 5.56 and 5.83 (m, $\prec_H^H$), 5.87 (broad d, J = 10.0 Hz, C_2–H), 7.08 (dd, J = 0.8, 10.0 Hz, C_3–H); Mass (25 ev, 170°, direct): *m/e* 246 (M^+).

3,4α - *Epoxy* - 1,1 - *ethylenedioxy* - 5αH,6,11βH - *eudesm* - 6,13 - *olide* (**6**). A mixture of **5** (103 mg, 0.352 mmol) and *m*-chloroperbenzoic acid (64 mg, 0.371 mmol) in CH_2Cl_2 (5 ml) was allowed to stand at room temp. for 100 h. The mixture was poured into KI aq and extracted with $CHCl_3$ (3 × 10 ml). The extracts were washed with 0.2N $Na_2S_2O_3$ aq and sat $NaHCO_3$ aq and concentrated to give 109 mg (100%) of spectroscopic pure **6**, which was recrystallized from $CHCl_3$–ether (1:1) to give needles, m.p. 257° (dec.); ν_{max}^{KBr} 1772 cm^{-1}; δ 1.12 (s, C_{10}–Me), 1.23 (d, J = 6.5 Hz, C_{11}–Me), 1.49 (s, C_4–Me), 2.16 (1H, d, J = 3.0 Hz, C_2–H), 2.20 (1H, d, J = 1.5 Hz, C_2–H), 2.43 (d, J = 12.0 Hz, C_5–H), 3.01 (dd, J = 1.5, 3.0 Hz, C_3–H), 3.6–4.1 (m, $\left[\begin{matrix}O\\O\end{matrix}\right>$ and C_6–H). (Found: C, 66.26; H, 7.89. $C_{17}H_{24}O_5$ requires: C, 66.21; H, 7.85%).

1 - *Oxo* - 5αH,6,11βH - *eudesm* - 2,4(14) - *dien* - 6,13 - *olide* (**7**) *from* **6**. A soln of **6** (50 mg, 0.162 mmol) in 50% AcOH aq (5 ml) was refluxed for 65 hr. The mixture was poured into sat NaCl aq and extracted with EtOAc (2 × 10 ml). The extracts were washed with sat $NaHCO_3$ aq and sat NaCl aq, dried (Na_2SO_4) and concentrated *in vacuo*. The residue (37 mg) was purified by preparative TLC [silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1:9)]. The first band (R_f 0.44) gave 20 mg (36.1%) of **7**. The second band (R_f 0.09) gave 18 mg (30.3%) of vulgarin.

1 - *Oxo* - 5αH,6,11βH - *eudesm* - 4(14) - *en* - 6,13 - *olide* (**8**). Fine Zn powder (210 mg) was treated with 3N HCl (0.62 ml) for 1 min, decanted off and activated by shaking with a soln of $HgCl_2$ (33 mg) in 0.6N HCl (0.45 ml). After 1 min the mixture was decanted off and the residual Zn was added into a soln of **7** (42 mg, 0.171 mmol). The mixture was refluxed for 2 h, cooled and filtered. The filtrate was poured into sat NaCl aq (10 ml) and extracted with $CHCl_3$. The extract was washed with sat $NaHCO_3$ aq and sat NaCl aq, dried (Na_2SO_4) and concentrated to give 38 mg of crude crystalline material, which was chromatographed over silica gel (Merck, < 230 mesh, 4 g) and eluted with $CHCl_3$ to give 29 mg (68.5%) of spectroscopic pure **8**, $\nu_{max}^{CHCl_3}$ 1703 cm^{-1}; δ 1.13 (s, C_{10}–Me), 1.23 (d, J = 6.7 Hz, C_{11}–Me), 4.13 (t, J = 10.0 Hz, C_6–H), 5.10 and 5.22 (m, $\prec_H^H$).

1β - *Hydroxy* - 5αH,6,11βH - *eudesm* - 4(14) - *en* - 6,13 - *olide* (**9**). A mixture of **8** (32 mg, 0.129 mmol) and $LiAlH(tBuO)_3$ (93 mg, 0.366 mmol) in dry THF (3 ml) was stirred for 2 h at 0°. The reaction was quenched by addition of 2N HCl (1 ml) and the mixture was extracted with EtOAc (3 × 10 ml). The extracts were washed with sat NaCl aq, dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue (36 mg) showed single spot (R_f 0.24) on TLC [silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1:9)]; δ 0.83 (s, C_{10}–Me), 1.22 (d, J = 6.5 Hz, C_{11}–Me), 3.51 (q, J = 5.0, 10.5 Hz, C_1–H), 4.08 (broad t, J = ca. 10 Hz, C_6–H), 4.83 and 4.99 (m, $\prec_H^H$). For the limited amounts of sample, this material was used in the next experiment without further purification.

1β - *Hydroxy* - 11β - *phenylseleno* - 5αH,6βH - *eudesm* - 4(14) - *en* - 6,13 - *olide* (**10**). To a dry THF soln of lithium diisopropylamide [prepared from diisopropylamine (44 μl, 0.317 mmol), 1.6 M BuLi (198 μl, 0.317 mmol) and dry THF (0.7 ml) at −78°] was added dropwise 36 mg (0.129 mmol) of **9** in dry THF (0.2 ml). After the soln was stirred at −78° for 1 h, diphenyl diselenide (98.8 mg, 0.317 mmol) in dry THF (0.3 ml) and HMPA (55 μl) was added dropwise at −78°. The mixture was stirred at −78° for 40 min, then warmed to −40° and kept at that temp. for 1 h. The reaction was quenched by addition of 0.6N HCl aq (1 ml). The mixture was extracted with EtOAc (2 × 10 ml). The extracts were washed with sat NaCl aq, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative TLC [silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1:9)]. The first band (R_f 0.58) gave diphenyl diselenide. The second band (R_f 0.45) gave an unidentified oily product. The third band (R_f 0.34) gave 16 mg (30.8% overall yield from **8**) of **10** as a crystalline material; δ 0.81 (s, C_{10}–Me), 1.53 (s, C_{11}–Me), 3.49 (q, J = 4.0, 10.0 Hz, C_1–H), 4.40 (t, J = 10.5 Hz, C_6–H), 4.72 and 4.93 (m, $\prec_H^H$), 7.2–7.8 (5H, $-C_6H_5$).

Reynosin (**1**). To a soln of **10** (16 mg, 0.040 mmol) in THF (0.3 ml) containing AcOH (6 μl, 0.100 mmol) cooled to 0° was added 30% H_2O_2 (27 μl). The mixture was stirred for 1 hr at 0°, then poured into cold sat $NaHCO_3$ aq and extracted with EtOAc. The extract was washed with sat NaCl aq, dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue was purified by preparative TLC [silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1:9)] to give 10 mg (quantitative yield) of spectroscopic pure reynosin as an oil, which was further purified by TLC in the same condition and then recrystallized from C_6H_6–cyclohexane (1:1) to give 5 mg of crystals, m.p. 145° (lit.[1] 145–146°); $\nu_{max}^{CHCl_3}$ 3610, 3500, 1765, 1670(w), 1650(w), cm^{-1}; δ (100 MHz) 0.83 (s, C_{10}–Me), *ca.* 2.6 (m, C_7–H), 3.57 (q, J = 4.5, 10.0 Hz, C_1–H), 4.06 (t, J = 10.8 Hz, C_6–H), 4.89 and 5.02 (m, $C_4{=}C_{14}$ ), 5.42 and 6.10 (d, J = 3.0 Hz, $C_{11}{=}C_{12}$ ). This material was identical with natural reynosin[1,2] in IR ($CHCl_3$) and NMR ($CDCl_3$).[11]

Vulgarin (**11**) *and* C_4*-epimer of vulgarin* (**12**) were synthesized in 5.86% and 3.56% yield from α-santonin respectively.[8] These materials showed the following data. Vulgarin, m.p. 174–175°; $\nu_{max}^{CHCl_3}$ 3480, 1770, 1660 cm^{-1}; δ 1.21 (s, C_{10}–Me), 1.24 (d, J = 6.5 Hz, C_{11}–Me), 1.56 (s, C_4–Me), 2.41 (d, J = 11.5 Hz, C_5–H), 4.15 (q, J = 9.5, 11.5 Hz, C_6–H), 5.84 (d, J = 10.5 Hz, C_2–H), 6.58 (d, J = 10.5 Hz, C_3–H). C_4-Epimer of vulgarin, m.p. 185–186°; ν_{max}^{KBr} 3540, 1785, 1773, 1680 cm^{-1}; δ 1.23 (d, J = 6.5 Hz, C_{11}–Me), 1.34 (s, C_{10}–Me), 1.58 (s, C_4–Me), 2.01 (d, J = 10.5 Hz, C_5–H), 4.36 (t, J = 10.5 Hz, C_6–H), 5.83 (d, J = 10.0 Hz, C_2–H), 6.51 (d, J = 10.0 Hz, C_3–H); Mass (25 eV, 70°, direct): *m/e* 264 (M^+). (Found: C, 67.67; H, 7.83. $C_{15}H_{20}O_4$ requires: C, 68.16; H, 7.63%).

1 - *Oxo* - 5α*H*,6,11β*H* - 3 - *en* - 6,13 - *olide* (**13**) *from* **11**.[12] Fine Zn powder (250 mg) was treated with 3N HCl (0.8 ml) for 1 min. The aqueous layer was decanted off and the residue was activated by shaking with a soln of $HgCl_2$ (40 mg) in 0.6N HCl (0.5 ml). After 1 min the aqueous layer was decanted off, Zn was washed with water and AcOH, and a soln of vulgarin (50 mg, 0.189 mmol) in AcOH (2.2 ml) was added. The mixture was stirred for 2 h under refluxing, cooled and filtered. The filtrate was poured into sat NaCl aq (10 ml) and extracted with $CHCl_3$ (4 × 10 ml). The extracts were washed with sat $NaHCO_3$ aq and sat NaCl aq, dried (Na_2SO_4) and concentrated to give 50 mg of a crystalline material, which was purified by preparative TLC [silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1:9)] to give 36 mg (76.7%) of **13** after washing with petroleum ether, m.p. 139° (lit.[12] 138–139°, 140–143°); $\nu_{max}^{CHCl_3}$ 1775, 1705 cm^{-1}; δ 1.17 (s, C_{10}–Me), 1.25 (d, J = 6.8 Hz, C_{11}–Me), 1.98 (m, C_4–Me), 2.89 (2H, m, C_7–H), 4.07 (dd, J = 10.0, 11.0 Hz, C_6–H), 5.57 (m, $W_{h/2}$ = 9.0 Hz, C_3–H).

1 - *Oxo* - 5α*H*,6,11β*H* - 3 - *en* - 6,13 - *olide* (**13**) *from* C_4*-epimer of Vulgarin* (**12**). Into the activated Zn powder (430 mg) which was prepared by the above mentioned method was added a soln of **12** (86 mg, 0.325 mmol) in AcOH (3.8 ml). The mixture was stirred for 2 h under refluxing, cooled and poured into sat NaCl aq (30 ml). The mixture was extracted with $CHCl_3$ (3 × 10 ml). The extracts were washed with sat $NaHCO_3$ aq and sat NaCl aq, dried (Na_2SO_4) and concentrated to give 85 mg of a crystalline material, which was separated by preparative TLC [silica gel GF_{254}, EtOAc–$CHCl_3$ (1:9)] to give 57 mg (70.6%) of **13**.

1β - *Hydroxy* - 5α*H*,6,11β*H* - 3 - *en* - 6,13 - *olide* (**14**). A mixture of **13** (30 mg, 0.121 mmol) and $LiAlH(tBuO)_3$ (91 mg, 0.358 mmol) in dry THF (3 ml) was stirred at 0° for 2 h and quenched by addition of 0.6N HCl (2 ml) at 0°. The mixture was poured into sat NaCl aq (20 ml) and extracted with EtOAc (3 × 10 ml). The extracts were washed with sat NaCl aq, dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue showed two spots (R_f 0.29, minor; R_f 0.24, major) on TLC [silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1:9)] and was purified by preparative TLC. The first band gave 10 mg of a mixture of **14** and **15** and the second band gave 20 mg (66.0%) of **14** as white crystals, m.p. 134.5°; δ 0.89 (s, C_{10}–Me), 1.21 (d, J = 6.5 Hz, C_{11}–Me), 1.82 (broad s, C_4–Me), 3.63 (dd, J = 7.0, 10.0 Hz, C_1–H), 3.97 (broad t, J = 10.0 Hz, C_6–H), 5.33 (m, $W_{h/2}$ = 8.0 Hz, C_3–H). In another experiment 57 mg (0.230 mmol) of **13** was reduced with $LiAlH(tBuO)_3$ (173 mg, 0.680 mmol) in THF (5.7 ml) at 0° to give 5:1 mixture of **14** and **15** (57 mg). This material was used for the starting material of the next step without further purification.

3,4α - *Epoxy* - 1β - *hydroxy* - 5α*H*,6β*H* - *eudesman* - 6,13 - *olide* (**16**) *and* 3,4α - *epoxy* - 1α - *hydroxy* - 5α*H*,6β*H* - *eudesman* - 6,13 - *olide* (**17**). A 5:1 mixture of **14** and **15** (67 mg, 0.268 mmol) was treated with *m*-$ClC_6H_4CO_3H$ (56 mg, 0.325 mmol) in CH_2Cl_2 (5 ml) for 7 days at room temp. The mixture was diluted with chloroform and filtered. The filtrate was washed with KI aq, $Na_2S_2O_3$ aq, sat $NaHCO_3$ aq and sat NaCl aq, dried (Na_2SO_4) and concentrated to give a crystalline product, which was purified by preparative TLC [silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1:19)]. The first band gave 9 mg (12.6%) of spectroscopic pure **17**, which was recrystallized from EtOH to give white crystals, m.p. 184–186°; δ 0.90 (s, C_{10}–Me), 1.23 (d, J = 6.8 Hz, C_{11}–Me), 1.50 (s, C_4–Me), 3.02 (m, $W_{h/2}$ = 4.0 Hz, C_3–H), 3.21 (m, $W_{h/2}$ = *ca.* 10, C_1–H), 3.73 (q, J = 8.5, 10.0 Hz, C_6–H); Mass (60°, 25 eV, direct): *m/e* 266 (M^+). The second band gave 48 mg (67.2%) of spectroscopic pure **16**, which was recrystallized from EtOH to give prisms, m.p. 195–195.5°; δ 0.93 (s, C_{10}–Me), 1.23 (d, J = 6.6 Hz, C_{11}–Me), 1.46 (s, C_4–Me), 3.01 (dd, J = 0.8, 3.3 Hz, C_3–H), 3.43 (dd, J = 6.5, 10.0 Hz, C_1–H), 3.93 (dd, J = 9.0, 11.0 Hz, C_6–H); Mass (80°, 25 eV, direct): *m/e* 266 (M^+).

3,4α - *Epoxy* - 1β - *hydroxy* - 11β - *phenylseleno* - 5α*H*,6β*H* - *eudesman* - 6,13 - *olide* (**18**). To a dry THF soln of lithium diisopropylamide [prepared from diisopropylamine (60 μl, 0.430 mmol), 1.60 M BuLi (0.28 ml, 0.448 mmol) and dry THF (2 ml) at −78°] was added dropwise over a period of 30 min 37 mg (0.139 mmol) of **18** in 1 ml of THF. After the soln was stirred at −78° for 1 hr, diphenyl diselenide (136 mg, 0.436 mmol) in dry THF (1 ml) and HMPA (76 μl) was added dropwise at −78°. The mixture was stirred at −78° for 15 min, then warmed to −40° and kept at that temp. for 1.5 h. The reaction was quenched by addition of 0.6N HCl aq (2.5 ml). The mixture was extracted with EtOAc (2 × 10 ml). The extracts were washed with sat NaCl aq, dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue showed two spots on TLC (silica gel GF_{254}, EtOAc). The first band (R_f 0.68) gave dipheny diselenide. The second band (R_f 0.44) gave 50 mg (85.4%) of **18** as an oil; δ 0.89 (s, C_{10}–Me), 1.36 (s, C_4–Me), 1.55 (s, C_{11}–Me), 2.97 (d, J = 3.0 Hz, C_3–H), 3.37 (dd, J = 6.5, 10.0 Hz, C_1–H), 4.21 (dd, J = 10.0, 11.5 Hz, C_6–H), 7.2–7.8 (5H, $-C_6H_5$).

Epoxysantamarine (**3**). To a soln of **18** (50 mg, 0.119 mmol) in THF (0.6 ml) containing AcOH (18 μl) cooled at 0° was added 30% H_2O_2 (85 μl, 0.986 mmol). The mixture was stirred for 30 min at 0°, then poured into cold sat $NaHCO_3$ aq and extracted with chloroform (3 × 10 ml). The extracts were washed with sat NaCl aq, dried (Na_2SO_4) and concentrated to give 27 mg (85.8%) of white crystals, which was identical with natural epoxysantamarine in NMR (60 MHz, DMSO d_6)[11] and showed single spot (R_f 0.48) on TLC (silica gel GF_{254}, thickness 0.25 mm, EtOAc). This material was recrystallized from EtOH to give 22 mg of prisms, m.p. 243–248° (dec) [lit.[1] 243–246° (dec)]; ν_{max}^{KBr} 3410, 1758, 1670(w) cm^{-1}; δ (100 MHz, DMSO d_6) 0.81 (s, C_{10}–Me), 1.35 (s, C_4–Me), 2.62 (m, C_7–H), 2.97 (d, J = 3.0 Hz, C_3–H), 3.16 (ddd, J = 5.5, 6.5, 10.0 Hz, C_1–H), 4.07 (dd, J = 10.5, 11.5 Hz, C_6–H), 4.59 (d, J = 5.5 Hz, –OH), 5.50 and 5.92 (d, J = 3.0 Hz, $\prec_{H}^{H}$).

4α - *Hydroxy* - 1 - *oxo* - 5α*H*,6,11β*H* - *eudesman* - 6,13 - *olide* (**19**). A soln of 44 mg (0.166 mmol) of vulgarin in EtOAc (4 ml) was hydrogenated in the presence of 10% Pd/C (13 mg). After 2.5 h the catalyst was removed and the filtrate was concentrated *in vacuo*. The crystalline residue was purified by TLC [silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1:9)] to give 42 mg (95%) of **19**. This material was recrystallized from EtOH to give needles, m.p. 170–172° (lit.[12] 172–173°); ν_{max}^{KBr} 3540, 1770, 1700 cm^{-1}; δ 1.18 (s, C_{10}–Me), 1.22 (d, J = 6.5 Hz, C_{11}–Me), 1.52 (s, C_4–Me); 4.12 (t, J = 10.5 Hz, C_6–H). (Found: C, 67.81; H, 8.39. $C_{15}H_{22}O_4$ requires: C, 67.64; H, 8.33%).

1β,4α - *Dihydroxy* - 5αH,6,11βH - *eudesman* - 6,13 - *olide* (**20**). To a soln of **19** (37 mg, 0.139 mmol) was added $NaBH_4$ 7.6 mg, 0.201 mmol). The mixture was stirred for 1 h at 0° and poured into 10 ml of sat NaCl aq. The soln was extracted with EtOAc (4 × 5 ml). The extracts were washed with sat NaCl aq, dried (Na_2SO_4) and concentrated to give 37 mg of an oil, which was purified by TLC (silica gel GF_{254}, thickness 0.25 mm, EtOAc) and recrystallization from EtOAc to give 21 mg (56.3%) of **20**, m.p. 197° (lit.[12] 197–199°); δ 0.99 (s, C_{10}–Me), 1.23 (d, J = 6.5 Hz, C_{11}–Me), 1.36 (s, C_4–Me), 3.38 (m, $W_{h/2}$ = *ca.* 13, C_1–H), 3.70 (1H, –OH), *ca.* 4.1 (2H, m, C_6–H, –OH). In another experiment 62 mg (0.233 mmol) of **19** was reduced with $NaBH_4$ (12.6 mg, 0.333 mmol) to give 63 mg of crude product, which was used as the starting material of the next reaction.

1β,4α - *Dihydroxy* - 11β - *phenylseleno* - 5αH,6βH - *eudesman* - 6,13 - *olide* (**21**). To a dry THF soln of lithium diisopropylamide [prepared from diisopropylamine (119 μl, 0.850 mmol), 1.7 M BuLi (500 μl, 0.850 mmol) and dry THF (2 ml) at −78°] was added dropwise over a period of 15 min, 40.5 mg (0.151 mmol) of **20** in THF (1 ml). After the soln was stirred at −78° for 1 h diphenyl diselenide (265 mg, 0.850 mmol) in dry THF (1.4 ml) and HMPA (157 μl, 0.850 mmol) was added dropwise at −78°. The mixture was stirred at −78° for 15 min, then warmed to −40° and kept at that temp. for 1 h. The reaction was quenched by addition of 0.1N HCl (18 ml). The mixture was stirred at −20° for 30 min and extracted with EtOAc (3 × 10 ml). The extracts were washed with sat NaCl aq, dried (Na_2SO_4) and concentrated to give 300 mg of crude product, which was purified by TLC [silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1:9)]. The first band (R_f 0.63) gave 200 mg of diphenyl diselenide. The second and third band (R_f 0.45 and 0.35) gave 9 mg of unidentified products. The fourth band gave 33 mg (51.6% overall yield from **19**) of **21** as an oil; δ 0.97 (s, C_{10}–Me), 1.28 (s, C_4–Me), 1.56 (s, C_{11}–Me), 3.38 (m, C_1–H), 4.40 (t, J = 9.5 Hz, C_6–H), 7.13–7.80 (5H, $-C_6H_5$).

1β-*Hydroxyarbusculin A*. To a soln of **21** (33 mg, 0.078 mmol) in THF (0.4 ml) containing AcOH (11 μl) cooled to 0° was added 30% H_2O_2 (52 μl, 0.603 mmol). The mixture was stirred for 45 min at 0°, then poured into cold sat NaCl aq and extracted with $CHCl_3$ (3 × 10 ml). The extracts were washed with sat NaCl aq, dried (Na_2SO_4) and concentrated to give 20 mg of a crystalline material, which was purified by TLC (silica gel GF_{254}, thickness 0.25 mm, EtOAc) to give 18 mg (86.8%) of 1β-hydroxyarbusculin A (R_f 0.19), which was recrystallized from EtOH to give prisms, m.p. 194–196° (lit.[2] 194–196°); $\nu_{max}^{CHCl_3}$ 3580, 3460, 1775 cm^{-1}; δ (100 MHz) 0.99 (s, C_{10}–Me), 1.36 (s, C_4–Me), 2.60 (m, C_7–H), 3.10 (m, –OH), 3.42 (m, C_1–H), 4.12 (t, J = 11.2 Hz, C_6–H).

Acknowledgement—We thank Prof. V. Herout for the kind supply of IR and NMR spectra of reynosin and 1β-hydroxyarbusculin A.

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