Studies on the Syntheses of Sesquiterpene Lactones. I. Chemical Transformation of α-Santonin into Vulgarin, C_4-Epivulgarin, and Arglanine*

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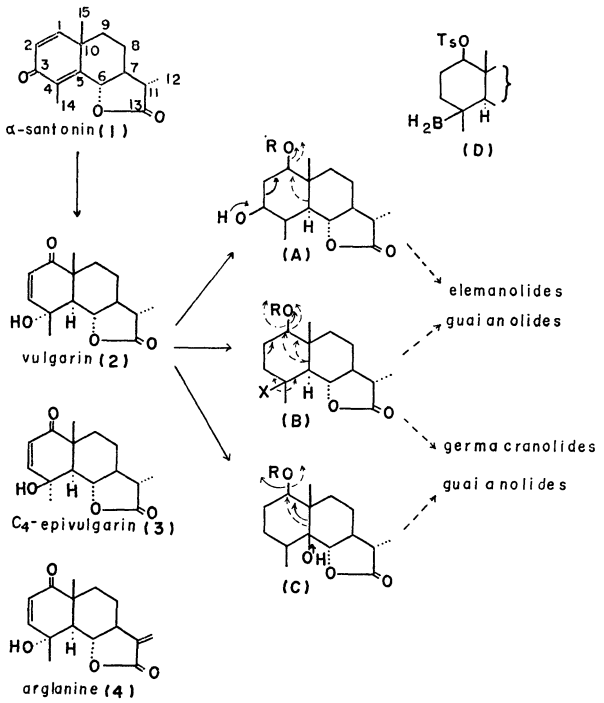
Syntheses of vulgarin, C_4-epivulgarin, and arglanine are reported. An efficient conversion of 3-oxo-5αH, 4β,6β, 11βH-eudesm-1-en-6,13-olide into 1-oxo-5αH,4β,6β,11βH-eudesm-2-en-6,13-olide, a key intermediate of these syntheses, was achieved by the Meerwein-Ponndorf reaction and the allylic rearrangement of the resultant 3-hydroxyl derivative followed by the Collins oxidation. Acetalization of 1-oxo-5αH,4β,6β,11βH-eudesm-2-en-6,13-olide and successive isomerization of the double bond gave 1,1-ethylenedioxy-5αH,6β,11βH-eudesm-3-en-6,13-olide regioselectevity. Oxidation of this compound with OsO_4 gave 3α,4α-dihydroxy-1,1-ethylenedioxy-5αH,6β,11βH-eudesman-6,13-olide, 3α,4α-dihydroxy-1-oxo-5αH,6β,11βH-eudesman-6,13-olide and 3β,4β-dihydroxy-1,1-ethylenedioxy-5αH,6β,11βH-eudesman-6,13-olide. Oxidation of 1,1-ethylenedioxy-5αH,6β,11βH-eudesm-3-en-6,13-olide with *m*-chloroperoxybenzoic acid gave 3α,4α-epoxy-1,1-ethylenedioxy-5αH,6β,11βH-eudesm-6,13-olide stereoselectively in a quantitative yield. Treatment of 3α,4α-dihydroxy-1,1-ethylenedioxy-5αH,6β,11βH-eudesman-6,13-olide,3α,4α-dihydroxy-1-oxo-5αH,6β,11βH-eudesman-6,13-olide, and 3α,4α-epoxy-1,1-ethylenedioxy-5αH,6β,11βH-eudesm-6,13-olide with boiling 50% AcOH gave vulgarin. The same treatment of 3β,4β-dihydroxy-1,1-ethylenedioxy-5αH,6β,11βH-eudesman-6,13-olide gave C_4-epivulgarin. Phenylselenenylation of 3α,4α-dihydroxy-1,1-ethylenedioxy-5αH,6β,11βH-eudesman-6,13-olide and successive syn-elimination of the resultant phenylseleno lactone gave 3α,4α-dihydroxy-1,1-ethylenedioxy-5αH,6βH-eudesm-11-en-6,13-olide, which was transformed into arglanine by treatment with boiling 50% AcOH.

The sesquiterpene lactones with α-methylene-γ-lactone moiety fused on various skeletons are a rapidly expanding group of natural products, comprising to date more than 400 varieties.[1] These unsaturated lactones have considerable biological activities as allergenic agents,[2] cytotoxic and antitumor agents,[3] regulators of plant growth and antimitotic activity,[4] and antischistosomal agents.[5] In all these cases, the α-methylene-γ-lactone unit has been assigned a central role in the activity mechanism.

Efficient syntheses of these sesquiterpene lactones are a synthetic challenge which has received much attention during the past few years.[6] For the general syntheses of these sesquiterpene lactones with various skeletons, we envisioned approaches which consisted of the solvolytic rearrangements or the fragmentation reactions of the appropriately functionalized eudesmanolides, such as compounds (**A**), (**B**), and (**C**), as shown in Scheme 1. Solvolytic rearrangements of cis- and trans-decalin derivatives with an equatorial hydroxyl group at C_1 have been applied to the syntheses of guaiane-type sesquiterpenes with rather simple structures, such as bulnesol, bulnesene, and kessane.[7] The fragmentation reaction of alkyl borane derivatives[8] with a partial structure (**D**) is a well-documented reaction and has been applied to the syntheses of hedycaryol. The fragmentation of 1,4a-decalindiol monosulfonates[9] has provided an efficient route to cyclodecenones. But these solvolytic rearrangements or fragmentation reactions have not yet been applied to the syntheses of guaianolides, germacranolides, and elemanolides, probably because of the difficulties of the syntheses of appropriately functionalized eudesmanolides such as **A**, **B**, and **C**. For the syntheses of these compounds, vulgarin



Scheme 1.

(**2**) and the related compounds are considered to be useful materials. Since vulgarin available from a natural source is limited,[10] and no practical synthesis of this compound has so far been reported, we have decided to examine the syntheses of vulgarin and related compounds. In the present paper we wish to report the efficient syntheses of vulgarin (**2**),[11] C_4-epivulgarin (**3**), and arglanine (**4**),[12] from α-santonin (**1**).

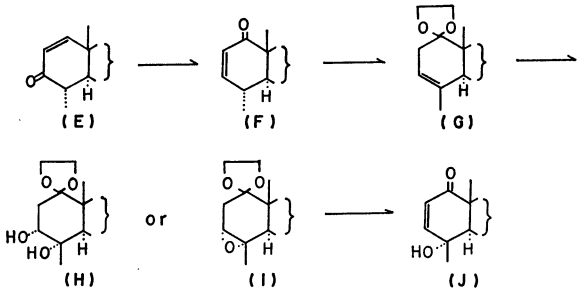
Results and Discussion

Synthesis of Vulgarin and C_4-Epivulgarin. Although one synthesis of vulgarin has been reported,[13] its final

* A preliminary report of this work was presented at the 34th Annual Meeting of the Chemical Sciety of Japan, Tokyo, April, 1976.

stages were carried out without the isolation or purification of intermediates and in very poor yield (0.5% in the last two steps). We wish to report the improved syntheses of vulgarin by two different routes starting from the α,β-unsaturated ketone (**5**) which was prepared from α-santonin by the known procedure.[14]

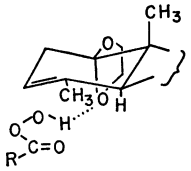
We envisioned an approach which consisted of the transfer of the oxygen function at C_3 of **5** into C_1 (**E**→**F**), protection of the carbonyl group and successive isomerization of the double bond (**F**→**G**), stereoselective oxidation of the double bond (**G**→**H** or **I**), and their transformation into vulgarin by deacetalization and simultaneous dehydration or acid-promoted opening of the epoxide (**H** or **I**→**J**).



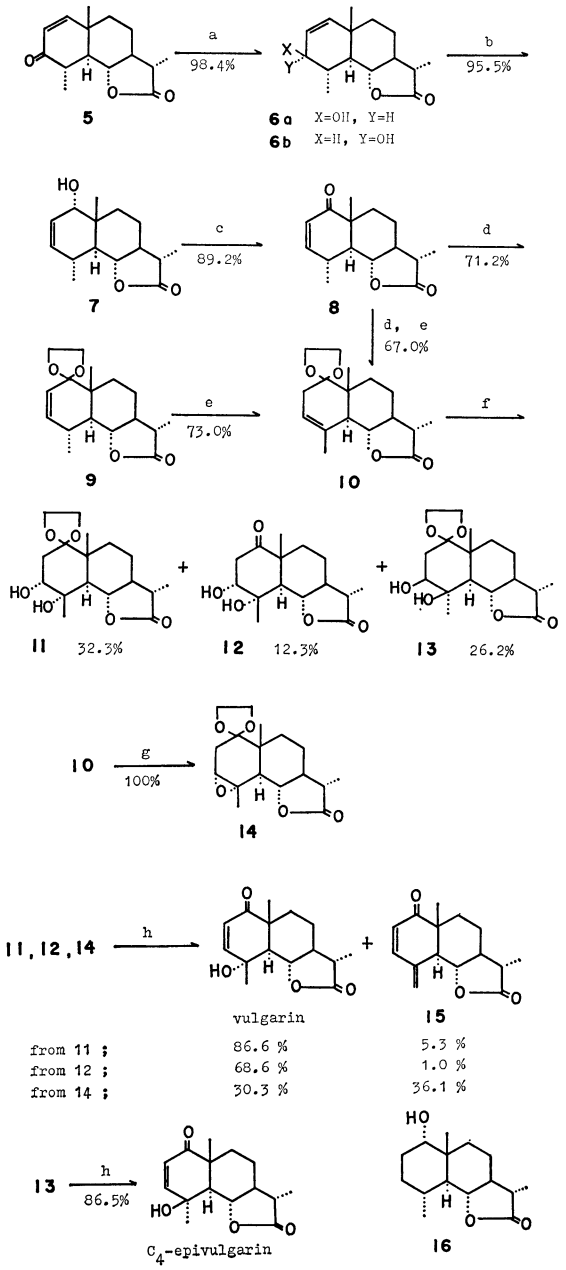
The Wharton rearrangement,[15] which involves the epoxidation of α,β-unsaturated ketone with hydrogen peroxide in alkali solution followed by the reduction of the resultant α,β-epoxy ketone with hydrazine, is a well-known reaction for the purpose of transferring the oxygen function from C_3 into C_1. Application of this method to **5** gave the desired alcohol (**7**) in poor yield (*ca.* 20%) because the γ-lactone moiety was sensitive to the reaction conditions. An efficient conversion of **5** to **7** was achieved by an alternative way. The Meerwein-Ponndorf reaction of **5** gave a 4 : 1 mixture of an allyl alcohol (**6a**) and its C_3-epimer (**6b**) in 98.4% yield.[16] Allylic rearrangement of this mixture by refluxing in THF containing 2 M HCl gave the desired allyl alcohol (**7**) stereoselectively in 78.5% yield, along with the recovery of the starting material (**6**) in 17.8% yield. (The conversion yield of **7** based on the starting material consumed was 95.5%.) The predominant formation of Δ^2-derivative (**7**) in this equilibrium reaction starting from Δ^1-derivative (**6**) is consistent with the fact that in *trans*-decalin series or 5α-steroid series Δ^2-derivatives are thermodynamically more stable than the corresponding Δ^1-derivatives.[17] α(ax)-Configuration of the hydroxyl group at C_1 in **7** was confirmed by the NMR spectrum of its dihydro derivative (**16**), which showed a peak at δ 3.37 (t, J=2.5 Hz, C_1–H) ppm. Oxidation of **7** by the Collins procedure gave an α,β-unsaturated ketone (**8**) in 89.2% yield. In agreement with the structure (**8**) the product exhibited an IR ($CHCl_3$) absorption at 1674 cm^{-1} and the NMR spectrum showed peaks at δ 5.85 (dd, J= 2.5 and 10.0 Hz, C_2–H) and 6.59 (dd, J=2.0 and 10.0 Hz, C_3–H) ppm.

Having completed the conversion of **5** to **8** in a sufficient yield (83.8%), we turned our attention to the problem of the isomerization of the double bond. Acetalization of **8** in a standard condition gave an acetal (**9**) in 71.2% yield.[18] Since it was expected that the acetal (**9**) with disubstituted double bond could be isomerized to the acetal (**10**) with a more stable trisubstituted double bond, the conditions of this isomerization reaction were investigated carefully; the best result was given by the following procedure. The double bond of **9** was isomerized by heating in ethylene glycol in the presence of *p*-toluensulfonic acid at 145 °C for 10 min, yielding **10** in 73.0%. No other double bond isomer of **10** was detected in these conditions.[19] The acetal (**10**) was also prepared in 67.0% overall yield from **8** without isolation of **9**.

Oxidation of the double bond of **10** was carried out by two different procedures and gave different results. Oxidation of **10** with osmium tetraoxide and successive treatment with hydrogen sulfide gave a mixture of an acetal (**11**) (32.3%), a ketone (**12**) (12.3%), and an acetal (**13**) (26.2%). Their stereochemistry was deduced from the coupling constant of C_3–H in their NMR spectra, as well as from the manner of reaction with osmium tetraoxide (cis addition). Since the 1,3-diaxial interaction between the 1α-oxygen of the acetal group and the entering reagent is expected in **10** because of the presence of the acetal group at C_1, the 1 : 1.7 ratio of the β face attack product (**13**) and the α face attack product (**11**+**12**) can be reasonably explained in terms of the competitive steric hindrance of the angular methyl group and the 1α-oxygen of the acetal group to the entering reagent. On the other hand, the epoxidation of **10** with *m*-chloroperoxybenzoic acid in dichloromethane proceeded stereoselectively from the α face to give 3α,4α-epoxide (**14**) in a quantitative yield. The difference of stereoselectivities between the osmylation and the epoxidation of **10** cannot be explained by simple steric factors. Probably the hydrogen-bonding interaction between *m*-chloroperoxybenzoic acid and the 1α-oxygen of the acetal group directs the α face attack of the reagent, as shown below.



Finally, the syntheses of vulgarin and C_4-epivulgarin have been completed by deacetalization and/or selective dehydration of the C_3-hydroxyl group of **11**, **12** and **13** or deacetalization and simultaneous ring opening of the epoxide (**14**). Deacetalization and selective dehydration of the C_3-hydroxyl group of **11** was accomplished by treatment with boiling 50% aqueous acetic acid for 74 h to give vulgarin in 86.6% yield. The same treatment of **12** gave vulgarin in 68.6% yield by dehydration of the C_3-hydroxyl group. The deacetalization and simultaneous opening of the epoxide ring of **14** to the expected direction was also accomplished by treatment with boiling 50% aqueous acetic acid for 65 h to give vulgarin in 30.3% yield, along with a 36.1% yield of dienone (**15**). The synthetic material was identical with the natural product in its melting point and NMR ($CDCl_3$) and IR ($CHCl_3$) spectra.[11,20] On the other hand, treatment of **13** with

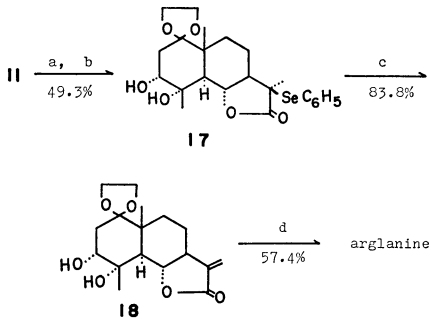


a: Al(*i*-PrO)$_3$, *i*-PrOH; b: 2 M HCl, THF; c: CrO_3·2Py, CH_2Cl_2; d: $HO(CH_2)_2OH$, *p*-TsOH, C_6H_6; e: Δ(145 °C), *p*-TsOH, $HO(CH_2)_2OH$; f: OsO_4, aq Dioxane, H_2S; g: *m*-$ClC_6H_4CO_3H$, CH_2Cl_2; h: 50% aq AcOH.

Scheme 2.

boiling 50% aqueous acetic acid for 72 h gave the C_4-epivulgarin (**3**) in 86.5% yield. The 1,3-diaxial relationship between C_4–OH and C_{10}–Me in this compound was clearly demonstrated in the NMR spectrum, in which the signal of C_{10}–Me appeared at 0.13 ppm lower field than the corresponding signal of vulgarin.[21]

Synthesis of Arglanine. Having completed the synthesis of vulgarin, we turned our attention to the synthesis of arglanine (**4**) with an α-methylene-γ-lactone group. Recently Yamakawa *et al.* reported the chemical transformation of α-santonin into arglanine.[22] We want to report here our independent result of the synthesis of arglanine. The convenient intermediate for this purpose was the compound (**11**) in which the carbonyl group at C_1 was protected as the ethylene acetal. Conversion of α-methyl-γ-lactone group of **11** into α-methylene-γ-lactone group was accomplished by the Grieco's procedure.[23] Thus the phenylselenenylation of **11** with diphenyl diselenide afforded phenylseleno lactone (**17**) in 49.3% yield. Oxidative syn-elimination of **17** with H_2O_2 in THF–HOAc afforded α-methylene-γ-lactone derivative (**18**) in 83.8% yield. Deacetalization and successive dehydration of the C_3-hydroxyl group of **18** was accomplished by treatment with boiling 50% aqueous acetic acid for 71 h to give arglanine in 57.4% yield. The synthetic material was identical with the natural product in IR (KBr) and NMR (60 MHz, $CDCl_3$) spectra.[12]



a: LiN(*i*-Pr)$_2$, THF; b: $C_6H_5SeSeC_6H_5$, HMPA; c: 30% H_2O_2, AcOH; d: 50% aq AcOH.

Scheme 3.

As the total synthesis of α-santonin has been accomplished,[24] the syntheses of vulgarin, C_4-epivulgarin, and arglanine reported in this paper are the formal total synthesis of these compounds. The investigation of the chemical transformations of vulgarin and related compounds into eudesmane-type α-methylene-γ-lactones,[25] guaiane-type α-methylene-γ-lactones, germacrane-type α-methylene-γ-lactones, and elemane-type α-methylene-γ-lactones are now in progress and will be reported elsewhere.

Experimental

All the melting points were uncorrected. IR spectra were determined on a Shimadzu IRG-I spectrometer. NMR spectra were recorded on Varian A-60 and HA-100 spectrometers in $CDCl_3$ containing TMS as internal standard. Mass spectra were recorded on a Hitachi RMU-6D spectrometer with a direct inlet system operating at 25 eV.

*3-Hydroxy-5αH,4β,6β,11βH-eudesm-1-en-6,13-olide (**6**).* A solution of 3-oxo-5αH,4β,6β,11βH-eudesm-1-en-6,13-olide (**5**, 1.32 g, 5.32 mmol) and Al(*i*-PrO)$_3$ (5.00 g, 23.90 mmol) in dry *i*-PrOH (80 ml) was allowed to boil gently in a 200 ml flask fitted with a Vigreux column. The acetone vapor formed was allowed to escape from the reaction mixture. After 4 h *i*-PrOH was distilled and the reaction mixture was reduced to *ca.* a 10 ml volume. Cold 2 M HCl (75 ml) was added, and the resulting acidic solution was extracted with EtOAc. The combined extracts were washed successively with sat $NaHCO_3$ aq and sat NaCl aq, dried (Na_2SO_4), and concentrated *in vacuo* to give 1.31 g (98.4%) of *ca.* 4 : 1

mixture of 3β-hydroxy-5αH,4β,6β,11βH-eudesm-1-en-6,13-olide (**6a**) and 3α-hydroxy-5αH,4β,6β,11βH-eudesm-1-en-6,13-olide (**6b**) as a mixture of plates and needles; mp 159—165 °C. IR (KBr): 3510 and 1750 cm^{-1}. NMR: δ 5.57 (s, 1.6H, C_1- and C_2-H of **6a**) and 5.71 (m, 0.4H, C_1- and C_2-H of **6b**) ppm. Found: C, 71.49; H, 9.26%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

*1α-Hydroxy-5αH,4β,6β,11βH-eudesm-2-en-6,13-olide (**7**).* A solution of **6** (1096 mg, 4.25 mmol) in a mixture of THF (95 ml) and 2 M HCl (63 ml) was refluxed under N_2 for 16 h, cooled, and poured into sat NaCl aq (150 ml). The mixture was extracted with $CHCl_3$ (50 ml×3). The combined extracts were washed successively with sat $NaHCO_3$ aq and sat NaCl aq, dried (Na_2SO_4), and concentrated *in vacuo* to give an oily crude product, which was chromatographed over silica gel (Merck, 70—230 mesh, 60 g) and eluated with CCl_4–$CHCl_3$ (2 : 1). The first running gave 40 mg of 1α-chloro-5αH,4β,6β,11βH-eudesm-2-en-6,13-olide, which was recrystallized from $CHCl_3$-ether (1 : 1) to give 20 mg of colorless needles; mp 218—219 °C. IR (KBr); 1770 and 778 cm^{-1}. NMR (100 MHz): δ 1.06 (3H, s, C_{10}–Me), 1.23 (3H, d, J=6.5 Hz, C_4- or C_{11}–Me), 1.24 (3H, d, J=6.5 Hz, C_4- or C_{11}–Me), 3.83 (1H, t, J=10.0 Hz, C_6–H), 4.07 (1H, broad d, J=5.5 Hz, C_1–H), 5.58 (1H, broad d, J=10.0 Hz, C_3–H), and 5.82 (1H, broad q, J=5.5 and 10.0 Hz, C_2–H) ppm. Found: C, 66.68; H, 7.91%. Calcd for $C_{15}H_{21}O_2Cl$: C, 66.97; H, 7.87%. The second running gave 850 mg (78.5%) of **7** as an amorphous substance: mp 138 °C. IR (KBr): 3600, 3400, 1765, and 742 cm^{-1}. NMR; δ 0.90 (3H, s, C_{10}–Me), 1.22 (6H, d, J=6.5 Hz, C_4- and C_{11}–Me), 3.46 (1H, d, J=5.0 Hz, C_1–H), 3.93 (1H, t, J=10.0 Hz, C_6–H), and 5.5—6.1 (2H, m, C_2- and C_3–H) ppm. Found: C, 71.08; H, 9.00%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

The third running gave 195 mg (17.8%) of recovered starting material, which was recrystallized from ether-$CHCl_3$ to give **6a** as colorless prisms; mp 180—181 °C. IR (KBr) 3530, 1758, and 752 cm^{-1}. NMR: δ 1.08 (3H, s, C_{10}–Me), 1.20 (3H, d, J=6.8 Hz, C_{11}–Me), 1.25 (3H, d, J=6.0 Hz, C_4–Me), 2.46 (1H, s, -OH), 3.82 (1H, d, J=8.0 Hz, C_3–H), 3.93 (1H, m, $W_{h/2}$=17.0 Hz, C_6–H), 5.58 (2H, s, C_1- and C_2–H) ppm.

*1-Oxo-5αH,4β,6β,11βH-eudesm-2-en-6,13-olide (**8**).* CrO_3 (5.12 g, 51.2 mmol) was added in small portions into a mixture of dry pyridine (10.5 ml, 103 mmol) and dry CH_2Cl_2 (65 ml) at 0 °C and stirred for 10 min. Then **7** (644 mg, 2.57 mmol) dissolved in CH_2Cl_2 (50 ml) was added, and the mixture was stirred at 0 °C for 6 h and filtered. The filtrate was washed successively with sat $NaHCO_3$ aq (30 ml×3), 2 M HCl (30 ml), and sat NaCl aq, dried (Na_2SO_4), and concentrated *in vacuo* to give 586 mg of crystalline material, which was chromatographed over silica gel (Merck, <230 mesh, 27 g) and eluted with CCl_4–$CHCl_3$ (1 : 1) to give 568 mg (89.2%) of **8**. This material (334 mg) was recrystallized from ether to give 206 mg of colorless prisms; mp 110—111 °C. IR (KBr): 1768, 1668, 812, and 738 cm^{-1}. NMR: δ 1.16 (3H, s, C_{10}–Me), 1.33 (6H, d, J=7.5 Hz, C_4- and C_{11}–Me), 4.01 (1H, t, J=10.0 Hz, C_6–H), 5.85 (1H, dd, J=2.5, 10.0 Hz, C_2–H), 6.59 (1H, dd, J=2.0, 10.0 Hz C_3–H) ppm. Found: C, 72.62; H, 8.33%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

*1,1-Ethylenedioxy-5αH,4β,6β,11βH-eudesm-2-en-6,13-olide (**9**).* A mixture of **8** (320 mg, 1.28 mmol), ethylene glycol (5 ml), and *p*-toluenesulfonic acid (38 mg) in dry C_6H_6 (60 ml) was refluxed in a flask equipped with a Dean-Stark column packed with molecular sieves for 24 h under N_2. The mixture was cooled and diluted with a mixture of sat NaCl aq and sat $NaHCO_3$ aq and the benzene layer was drawn off. The aqueous layer was further extracted with EtOAc. The combined extracts were washed with sat NaCl aq, dried (Na_2SO_4), and concentrated to give 408 mg of an oil, which was chromatographed over silica gel (Wakogel C-200, 20 g) and eluted with CCl_4–$CHCl_3$ (1 : 2) to give 268 mg (71.2%) of **9**. This material was recrystallized from ether to give a crystal; mp 148—152 °C. IR (KBr): 1777 and 745 cm^{-1}. NMR: δ 1.06 (3H, s, C_{10}–Me), 1.20 (6H, d, J=6.5 Hz, C_4- and C_{11}–Me), 3.5—4.2 (m, 5H, $|^{-O}_{-O}\rangle$ and C_6–H), 5.52 (2H, m, $W_{h/2}$=2.5 Hz, C_2- and C_3–H) ppm. Found: C, 69.74; H, 8.28%. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27%.

*1,1-Ethylenedioxy-5αH,6β,11βH-eudesm-3-en-6,13-olide (**10**) from **9**.* A mixture of **9** (140 mg), ethylene glycol (8 ml) and *p*-toluenesulfonic acid (17 mg) in dry C_6H_6 was refluxed in a flask equipped with a Dean-Stark column packed with molecular sieves for 1 h under N_2. C_6H_6 was removed and the residue was heated at 145 °C for 10 min under N_2, cooled, diluted with EtOAc, washed with sat NaCl aq, dried (Na_2SO_4) and concentrated to give a crude product which was chromatographed over silica gel (Merck, <230 mesh, 7 g) to give 102 mg (73%) of **10**.

*1,1-Ethylenedioxy-5αH,6β,11βH-eudesm-3-en-6,13-olide (**10**) from **8**.* A mixture of **8** (438 mg, 1.77 mmol), ethylene glycol (26 ml) and *p*-toluenesulfonic acid (52 mg) in dry C_6H_6 (100 ml) was refluxed in a flask equipped with a Dean-Stark column packed with molecular sieves for 23 h under N_2. C_6H_6 was removed and the residue was heated at 145 °C for 10 min under N_2, cooled, diluted with EtOAc, washed with sat NaCl aq, dried (Na_2SO_4), and concentrated to give an oily crude product (401 mg), which was chromatographed over silica gel (Merck, <230 mesh, 20 g) and eluted with CCl_4–$CHCl_3$ (1 : 1). The first running gave 345 mg (67.0%) of **10**, which was recrystallized from ether to give colorless prisms; 130—131 °C. IR ($CHCl_3$): 1765, 892, 863, and 852 cm^{-1}; NMR: δ 1.03 (3H, s, C_{10}–Me), 1.22 (3H, d, J=6.5 Hz, C_{11}–Me), 1.85 (3H, broad s, C_4–Me), 3.5—4.2 (m, 5H, $|^{-O}_{-O}\rangle$ and C_6–H), 5.29 (1H, m, $W_{h/2}$=7.0 Hz, C_3–H) ppm. Found: C, 69.70; H, 8.27%. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27%. The second running gave 47 mg of recovered **8**.

*Oxidation of **10** with Osmium Tetraoxide; Formation of 3α,4α-Dihydroxy-1,1-ethylenedioxy-5αH,6β,11βH-eudesman-6,13-olide (**11**), 3α,4α-Dihydroxy-1-oxo-5αH,6β,11βH-eudesman-6,13-olide (**12**), and 3β,4β-Dihydroxy-1,1-ethylenedioxy-5αH,6β,11βH-eudesman-6,13-olide (**13**).* To a solution of **10** (885 mg, 3.0 mmol) in dry dioxane (85 ml) was added OsO_4 (800 mg, 3.15 mmol). The mixture was allowed to stand at room temperature for 72 h, then saturated with hydrogen sulfide, and filtered through a layer of celite. The filtrate was poured into sat NaCl aq (250 ml) and extracted with chloroform (100 ml×3). The combined extracts were washed successively with sat $NaHCO_3$ aq (100 ml) and sat NaCl aq (100 ml), dried (Na_2SO_4), and concentrated to give a crude semisolidal product (903 mg) which showed three spots (R_f 0.45, 0.35, and 0.20) on TLC (silica gel GF_{254}, thichness 0.25 mm, EtOAc) and was purified by preparative TLC. The first band gave 256 mg (26.2%) of **13**, which was recrystallized from $CHCl_3$-ether (1 : 1) to give colorless prisms; mp 199—200 °C. IR ($CHCl_3$): 3560, 3460, and 1768 cm^{-1}. NMR: δ 1.17 (3H, d, J=7.0 Hz, C_{11}–Me), 1.27 (3H, s, C_{10}–Me), 1.46 (3H, s, C_4–Me), 2.61 (2H, m, -OH), 3.50 (1H, q, J=6.5, 10.5 Hz, C_3–H), 3.91 (4H, m, $|^{-O}_{-O}\rangle$), 4.23 (1H, m, $W_{h/2}$=*ca.* 18 Hz,

C_6–H) ppm. Found: C, 63.00; H, 8.28%. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.08%. The second band gave 104 mg (12.3%) of **12**, which was recrystallized from $CHCl_3$–ether (1 : 1) to give colorless prisms; mp 223 °C. IR (KBr) 3590, 3555, 1775, and 1718 cm^{-1}; NMR: δ 1.22 (3H, s, C_{10}–Me), 1.23 (3H, d, J=6.5 Hz, C_{11}–Me), 1.56 (3H, s, C_4–Me), 2.83—3.65 (2H, m, –OH), 3.92 (1H, t, J=4.0 Hz, C_3–H), 4.14 (1H, t, J=11.0 Hz, C_6–H). MS *m/e*: 282 (M^+). Found: C, 63.43; H, 7.88%. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85%. The third band gave 316 mg (32.3%) of **11**, which was recrystallized from $CHCl_3$–ether (1 : 1) to give colorless plates; mp 226—227 °C. IR ($CHCl_3$): 3480, 1782, and 1772 cm^{-1}: NMR: δ 1.14 (3H, s, C_{10}–Me), 1.20 (3H, d, J=6.5 Hz, C_{11}–Me), 1.34 (3H, s, C_4–Me), 3.62 (1H, m, $W_{h/2}$=6.0 Hz, C_3–H), 3.8—4.3 (5H, m, $\langle{}^{-O}_{-O}\rangle$ and C_6–H) ppm. After addition of D_2O, the signal at 3.62 ppm was changed to a triplet (J=3.4 Hz). Found: C, 62.53; H, 8.13%. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.08%.

Vulgarin (Tauremisin) from ***11***. A solution of **11** (225 mg, 0.69 mmol) in 50% AcOH aq (37 ml) was refluxed for 74 h under N_2, cooled, and poured into sat NaCl aq. The mixture was extracted with $CHCl_3$ (20 ml×3). The combined extracts were washed successively with sat $NaHCO_3$ aq (10 ml×2) and sat NaCl aq, dried (Na_2SO_4), and concentrated to give 181 mg of crude crystalline material, which showed two spots (R_f 0.38, minor; R_f 0.10, major) on TLC [silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1 : 9)]. This material was purified by preparative TLC [silica gel GF_{254}, EtOAc–$CHCl_3$ (1 : 9)]. The first band gave 9 mg of 1-oxo-5αH,6β,11βH-eudesm-2,4(14)-dien-6,13-olide (anhydrovulgarin, **15**) as an crystalline material. IR ($CHCl_3$): 1775, 1670, 927, and 840 cm^{-1}. NMR: δ 1.07 (3H, s, C_{10}–Me), 1.24 (3H, d, J=6.7 Hz, C_{11}–Me), 2.83 (1H, dt, J=10.0 and 1.8 Hz, C_5–H), 4.21 (1H, t, J=10.0 Hz, C_6–H), 5.56 and 5.83 (each, 1H, m, $=\langle{}^{H}_{H}$), 5.87 (1H, broad d, J=10.0 Hz, C_2–H), 7.08 (1H, dd, J=0.8 and 10.0 Hz, C_3–H) ppm. UV (MeOH) max: 268 nm. The second band gave 158 mg (86.6%) of vulgarin (Tauremisin), which was recrystallized from ethanol to give fine needles; mp 174—175 °C (lit, 174—175 °C). This material was identical with natural vulgarin in IR ($CHCl_3$) and NMR (60 MHz, $CDCl_3$).

Vulgarin from ***12***. A solution of **12** (56 mg, 0.199 mmol) in 50% AcOH aq (10 ml) was refluxed for 74 h under N_2, cooled, and poured into sat NaCl aq. The mixture was extracted with $CHCl_3$ (10 ml×3). The combined extracts were washed successively with sat $NaHCO_3$ aq, and sat NaCl aq, dried (Na_2SO_4), and concentrated to give 43 mg of crystalline material, which was purified by the combination of preparative TLC [silica gel GF_{254}, EtOAc–$CHCl_3$ (1 : 9)] and recrystallization from ethanol to give 36 mg (68.6%) of vulgarin and 0.5 mg of **15**.

C_4-Epimer of Vulgarin (4β-Hydroxy-1-oxo-5αH,6β,11βH-eudesm-2-en-6,13-olide, ***3***). A solution of **13** (100 mg, 0.307 mmol) in 50% AcOH aq (16 ml) was refluxed 72 h under N_2, cooled, and poured into sat NaCl aq. The mixture was extracted with chloroform (10 ml×3). The combined extracts were washed successively with sat $NaHCO_3$ aq (10 ml×2) and sat NaCl aq, dried (Na_2SO_4), and concentrated to give 95 mg of crystalline material, which was purified by preparative TLC [silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1 : 9), R_f 0.14] to give 70 mg (86.5%) of C_4 epimer of vulgarin (**3**). This material was recrystallized from EtOH to give colorless cubes; mp 185—186 °C. IR (KBr): 3540, 1773, and 1680 cm^{-1}. NMR: δ 1.23 (3H, d, J=6.5 Hz, C_{11}–Me), 1.34 (3H, s, C_{10}–Me), 1.58 (3H, s, C_4–Me), 2.01 (1H, d, J=10.5 Hz, C_5–H), 2.46 (1H, s, –OH), 4.36 (1H, t, J=10.5 Hz, C_6–H), 5.83 (1H, d, J=10.0 Hz, C_2–H), 6.51 (1H, d, J=10.0 Hz, C_3–H) ppm. MS *m/e*: 264 (M^+). Found: C, 67.67; H, 7.83%. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63%.

*3α,4α-Epoxy-1,1-ethylenedioxy-5αH,6β,11βH-eudesm-6,13-olide (****14****).* A mixture of **10** (103 mg, 0.35 mmol) and *m*-chloroperoxybenzoic acid (64 mg, 0.37 mmol) in CH_2Cl_2 (5 ml) was allowed to stand at room temperature for 100 h. The mixture was poured into KI aq and extracted with $CHCl_3$ (10 ml×3). The combined extracts were washed successively with 0.2 M $Na_2S_2O_3$ aq, sat $NaHCO_3$ aq, and sat NaCl aq, dried (Na_2SO_4), and concentrated to give 109 mg (100%) of spectroscopic pure **14**, which was recrystallized from $CHCl_3$–ether (1 : 1) to give colorless needles, mp 257 °C (dec). NMR: δ 1.12 (3H, s, C_{10}–Me), 1.23 (3H, d, J=6.5 Hz, C_{11}–Me), 1.49 (3H, 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 (1H, d, J=12.0 Hz, C_5–H), 3.01 (1H, dd, J=1.5 and 3.0 Hz, C_3–H), 3.6—4.1 (5H, m, $\langle{}^{-O}_{-O}\rangle$ and C_6–H). Found: C, 66.26; H, 7.89%. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85%.

Vulgarin and Anhydrovulgarin from ***14***. A solution of **14** (50 mg, 0.16 mmol) in 50% AcOH aq (5 ml) was refluxed for 65 h. The mixture was poured into sat NaCl aq and extracted with EtOAc (10 ml×2). The combined extracts were washed successively with sat $NaHCO_3$ aq and sat NaCl aq, dried (Na_2SO_4), and concentrated *in vacuo* to give 37 mg of crude product, which was purified by preparative TLC (silica gel GF_{254}, thickness 0.25 mm, EtOAc). The first band gave 20 mg (36.1%) of **15**. The second band gave 18 mg (30.3%) of vulgarin.

*3α,4α-Dihydroxy-1,1-ethylenedioxy-11β-phenylseleno-5αH,6βH-eudesman-6,13-olide (****17****).* To a dry THF solution of lithium diisopropylamide [prepared from diisopropylamine (77.4 μl, 0.72 mmol), 1.70 M butyllithium in hexane (0.43 ml, 0.72 mmol), and dry THF (1.8 ml) at −78 °C] was added dropwise over a period of 1h, 65 mg (0.2 mmol) of **11** in 2.0 ml of THF. After the solution was stirred at −78 °C for 40 min, diphenyl diselenide (225 mg, 0.72 mmol) in dry THF (1.2 ml) and HMPA (126 μl) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 40 min, then warmed to −40 °C and kept at that temperature for 1 h. The reaction was quenched by the addition of 0.1 M HCl aq (15 ml). The mixture was extracted with EtOAc (10 ml×2). The combined extracts were washed with sat NaCl aq, dried (Na_2SO_4), and concentrated to give 277 mg of product, which was purified by preparative TLC (silica gel GF_{254}, thickness 0.25 mm, EtOAc). The first band (R_f 0.64) gave 177 mg of diphenyl diselenide. The second band (R_f 0.14) gave 57 mg (49.3%) of **17**. NMR: δ 1.10 (3H, s, C_{10}–Me), 1.25 (3H, s, C_4–Me), 1.55 (3H, s, C_{11}–Me), 3.39 (1H, –OH), 3.66 (1H, m, C_3–H), 3.85 (1H, –OH), 3.97 (5H, m, $\langle{}^{-O}_{-O}\rangle$ and C_6–H), 7.2—7.8 (5H, m, $-C_6H_5$) ppm.

*3α,4α-Dihydroxy-1,1-ethylenedioxy-5αH,6βH-eudesm-11-en-6,13-olide (****18****).* To a solution of **17** (55 mg, 0.114 mmol) in THF (0.6 ml) containing acetic acid (17 μl) cooled to 0 °C was added 30% hydrogen peroxide (81 μl). The mixture was stirred for 30 min at 0 °C, then poured into cold sat $NaHCO_3$ aq and extracted with chloroform (10 ml×3). The combined extracts were washed with sat NaCl aq, dried (Na_2SO_4), and concentrated to give a crystalline material, which was purified by preparative TLC (silica gel GF_{254}, thickness 0.25 mm, EtOAc) to give 31 mg (83.8%) of **18** (R_f 0.20). NMR: δ 1.14 (3H, s, C_{10}–Me), 1.35 (3H, s,

C_4–Me), 3.45 (1H, –OH), 3.64 (1H, m, C_3–H), *ca.* 4.0 (6H, m, –OH, $\langle{}^{-O}_{-O}\rangle$, and C_6–H), 5.42 and 6.09 (each, 1H, d, J=3.0 Hz) ppm.

Arglanine (4). A solution of **18** (30 mg, 0.093 mmol) in 50% AcOH aq was refluxed for 71 h under N_2, cooled, and poured into sat NaCl aq (20 ml). The mixture was extracted with $CHCl_3$ (10 ml×2). The combined extracts were washed with sat $NaHCO_3$ aq (10 ml) and sat NaCl aq (10 ml), dried (Na_2SO_4), and concentrated to give a semi-solidal crude product. This was purified by preparative TLC (silica gel GF_{254}, EtOAc, thickness 0.25 mm) to give 14.0 mg (57.4%) of arglanine (R_f 0.52), which was recrystallized from EtOH to give colorless prisms, mp 190—192 °C. This material was identical with natural arglanine in IR (KBr) and NMR (60 MHz, $CDCl_3$).

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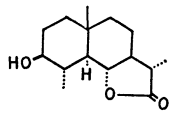
16) The major product (**6a**) was isolated by the combination of column chromatography over silica gel and recrystallization. β(eq)-Configuration of the hydroxyl group at C_3 in **6a** was deduced from its NMR spectrum, which showed a peak at δ 3.82 (broad d, J=8.0 Hz) ppm, and confirmed by the NMR spectrum of its dihydro derivative (**19**), which showed a peak at δ 3.09 (ddd, J=5.0, 9.5, and 9.5 Hz) ppm.



(19)

Although the attempted isolation of the minor product (**6b**) was unsuccessful, **6b** was deduced to be the C_3-epimer of **6a** from the fact that oxidation of the mixture of **6a** and **6b** gave **5** as the sole product.

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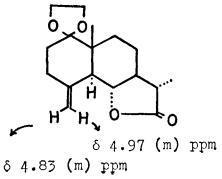
18) In mother liquors a small amount of **10** was observed, but the yield of **10** was not increased by prolonged reaction time under these conditions.

19) The double bond of **10** was further isomerized to the



exo double bond under more drastic conditions (higher reaction temperature or prolonged reaction time).

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