Stereoselective Synthesis of 4α-Hydroxy-8,12-Guaianolides from Santonin

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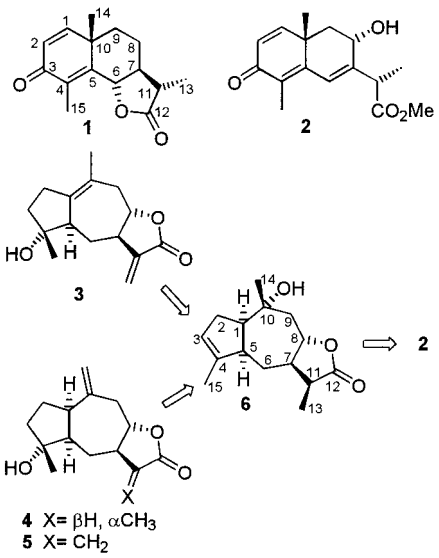
Hydroxyester **2**, easily obtained from santonin (**1**), has been transformed into 10α-hydroxyguai-3-en-8,12-olide **6**, a good intermediate for the synthesis of natural 8,12-guaianolides. Compound **6** was obtained from **2** by photochemical rearrangement of its acetyl derivative **7**, stereoselective hydrogenation on Pd/C, reduction, regioselective elimination, hydrolysis, and lactonization. The synthesis of the natural guaianolides **3**−**5** was carried out in two sequences in which the regioselective elimination of a hydroxyl group at C_{10} with triflic anhydride or $SOCl_2$ to afford, respectively, the endo or exo double bond on C_{10} and the regioselective opening of the C_3−C_4 α-epoxide were the key steps.

Guaiane sesquiterpenes including both 6,12- and 8,12-guaianolides make up a group of natural compounds widely present in the plant kingdom.[1] These natural products have aroused much interest on account of their wide spectrum of biological properties, particularly the cytotoxic and antitumor activity associated with the α-methylene-γ-lactone group.

Numerous syntheses of 6,12-guaianolides have been published starting from santonin (**1**),[1−3] a commercial natural product. However, there are few reports concerning the synthesis of 8,12-guaianolides. Barton et al. have reported a very low yield synthesis of the 8,12-guaianolide geigerin starting from artemisin, the 8α-hydroxy derivative of santonin (**1**).[4] The key step in these syntheses is the photochemical rearrangement from the eudesmane to the guaiane framework promoted by UV irradiation from the dienone moiety present in santonin or artemisin.[4,5]

In a previous paper, we described an efficient method for the funcionalization of C_8 in santonin to give alcohol **2**,[6] which has been proved a good intermediate for the synthesis of 8,12-eudesmanolides[6,7] and furanoeudesmanes.[8] As **2** presents in ring A the required dienone moiety for the photochemical rearrangement from eudesmane to guaiane,[9] we thought that this compound could also be useful for the synthesis of 8,12-guaianolides. Besides, since a number of natural 8,12-guaianolides, such as **3**−**5**, present a hydroxyl group at C_4 and different substitution at C_{10}, the 10α-hydroxyguai-3-en-8,12-olide **6** could be a good intermediate for the synthesis of these compounds.



In the present work we describe the synthesis of **6** using the easily available **2** as starting material and its transformation into the 4α-hydroxy-8,12-guaianolides **3**−**5**. Structure **3** was reported for 8-*epi*-pseudoivalin, a natural product isolated from *Helichrysum dasyanthum*[10]

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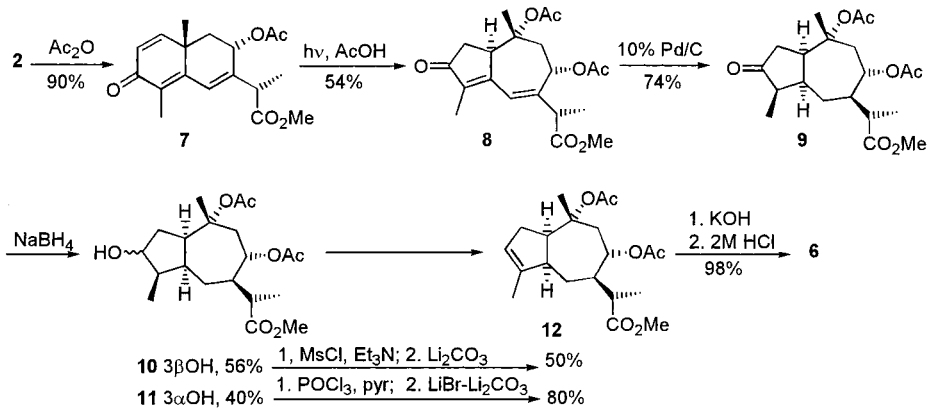
Scheme 1



and *Apalochlamys spectabilis*,[11] and guaianolide **4** and its 11,13-dehydro derivative **5** from *Dittrichia graveolens*.[12] Compound **5** has been also isolated from *Francoeuria crispa*,[13] *A. spectabilis*,[11] and *Inula anatolica*.[14]

Results and Discussion

For the synthesis of **6** (Scheme 1) the most important step was the change from a eudesmane to a guaiane framework by photochemical rearrangement in an acid medium of the dienone system. Since the selective hydrogenation of the C_6-C_7 double bond in the presence of the C_1-C_2 double bond seemed rather difficult, we decided to carry out this photochemical rearrangement on the trienone system, leaving the hydrogenation of the C_6-C_7 double bond for a further step. On the other hand, since it is known[15] that compound **2** in an acidic medium suffers lactone ring closure with concomitant migration of the double bond from C_6-C_7 to C_7-C_{11}, leading to a 8,12-butenolide, the C_8 hydroxyl group was protected as an acetate prior to irradiation in acetic acid.

Irradiation of an acetic acid solution of acetate **7** with UV light[16] for 9 h under argon gave the desired guaiane **8** (54%) in which the C_6-C_7 double bond remained unaltered, together with a significant amount of starting material **7** (22%). Unfortunately longer irradiation times did not increase the yield of **8** and diminished the amount of recovered starting material **7**.

The next step was the obtainment of the saturated ketone **9**. It was carried out by hydrogenation of compound **8** over 10% Pd/C in EtOH to give **9** (74%) with high stereoselectivity. No traces of other isomers were found in the reaction mixture. The structure and stereochemistry of compound **9** has been confirmed by the X-ray diffraction spectrum.

To form the C_3-C_4 double bond, the carbonyl group had to be reduced and the resulting alcohols eliminated. Treatment of **9** with $NaBH_4$ afforded the two epimeric alcohols **10** (56%) and **11** (40%), whose elimination was carried out in two steps and separately as they showed clear different reactivities toward halogenation or mesylation. Alcohol **10** by quick mesylation with MsCl in the presence of Et_3N and later elimination with Li_2CO_3 in DMF afforded alkene **12** (50%). On the other hand, treatment of its epimer **11** with $POCl_3$ in the presence of pyridine gave a mixture of epimeric chlorides (^{1}H NMR) which were subjected to elimination with Li_2CO_3-LiBr to also give compound **12** (80%). In this way **12** was obtained in 60% overall yield from **9**.

Finally the hydrolysis of the ester groups and lactonization were achieved by treatment with KOH in MeOH at rt and later acidification with 2 M HCl to give the expected guaianolide **6** in 98% yield.

With compound **6** in our hands we envisaged the synthesis of the natural guaianolides **3**−**5**. A 4α-OH could be introduced from the C_3-C_4 double bond, while regioselective elimination of the $C_{10}-OH$ would give rise to the endo- or exocyclic double bond. Further changes on the γ-lactone unity would allow the obtainment of the three natural compounds.

In the first instance we attempted the synthesis of compound **3**, which presents the double bond between C_1 and C_{10} (Scheme 2). As a tetrasubstituted double bond would react faster toward electrophilic reagents than the trisubstituted C_3-C_4, the first step was the epoxidation of this double bond. We subjected compound **6** to various epoxidation conditions [(*m*-CPBA,[17] dimethyldioxirane,[18] magnesium monoperphthalate (MMPP[19])]. In all cases mixtures of α- and β-epoxides were obtained in similar ratios (^{1}H NMR) without significant differences of stereoselectivity. As MMPP afforded the higher total yield, the reaction was carried out with this reagent, and a mixture of β-epoxide **13** (34%) and α-epoxide **14** (53%) was obtained. The stereochemistry of the oxirane rings was assigned by ^{1}H NMR on the basis of the chemical shift of the protons on C_6 with reference to those of compound **6**.[20] Proton H6α appears at similar δ values in compounds **6** (δ 1.98), **13** (δ 1.90), and **14** (δ 1.90), whereas in compound **13** H6β shows a downfield shift to δ 1.46 (δ 1.23 in **6**) due to the deshielding effect of the

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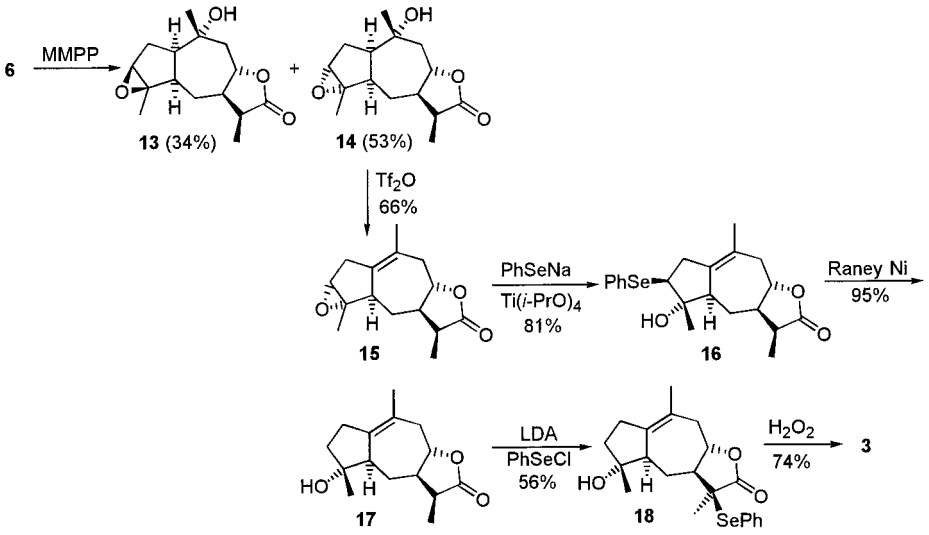
Scheme 2



oxirane ring. On the other hand, H6β shows a high-field shift in compound **14** (δ 1.05) which can be due to steric compression of the C_4-Me with a β disposition in the α-epoxide.

The formation of the C_1-C_{10} double bond was achieved regioselectively by treatment of compound **14** with triflic anhydride (Tf_2O)/pyridine in CH_2Cl_2 at rt[21] and afforded the expected tetrasubstituted alkene **15** in 66% yield. A positive NOE effect between C_4-Me and H6α indicated their spatial proximity and consequently the α diposition of the oxirane ring, as can be observed in a molecular model of this compound.

To open the oxirane ring, compound **15** was treated with PhSeNa/Ti(*i*-PrO)$_4$/DMF[22] and compound **16** was obtained in high yield (81%). Treatment of **16** with deactivated Raney Ni[23] effected the elimination of the phenylselenyl group and gave compound **17** in near quantitative yield (95%).

Finally conversion of **17** into the corresponding *exo*-methylene derivative **3** was achieved by Grieco's procedure.[24] Treatment of the lithium enolate of **17** with phenylselenyl chloride gave the phenylseleno derivative **18**, which after oxidative syn elimination with 30% H_2O_2 yielded **3** in 41% overall yield. Its NMR spectra were consistent with its structure and confirm this structure for natural 8-*epi*-pseudoivalin as the ^{1}H NMR spectral data were identical to the reported data for the natural product.[10,11]

For the synthesis of compounds **4** and **5** from **6** the new double bond should be introduced between C_{10} and C_{14}. In this case, treatment with excess $SOCl_2$ in pyridine, the reagent of choice in the literature,[2,25] should afford satisfactory yields for this elimination. Besides, as this gem-disubstituted double bond would react slower toward epoxidation than the trisubstituted C_3-C_4, the epoxidation and the elimination could be carried out in inverse order. Treatment of compound **6** by standard procedures ($SOCl_2$/pyridine−THF/−78 °C or rt)[25] afforded a mixture of the three possible alkenes (^{1}H NMR) (Scheme 3). Although the major constituent was the desired **19**, a significant amount of **20** with a C_9-C_{10} double bond was formed, while the C_1-C_{10} isomer could only be detected at a trace level. To increase the formation of the *exo*-methylene double bond, pyridine was substituted by more bulky bases (Et_3N, DBU) and the reaction carried out under different conditions. The highest selectivity was obtained with DBU (−60 °C, 20 min), which gave an 11:1 mixture of **19** (58%) and **20** (5%).

The epoxidation of **19** was carried out with MMPP[19] at 0 °C and afforded α-epoxide **21** in 61% yield with only 2% of its β-isomer **22** showing a higher stereoselectivity than the epoxidation of compound **6** to **14**. A clear deshielding effect of H6β in compound **22** (δ 1.30, 1.02 in **19**) allows us to assign the stereochemistry of these epoxides. The regioselective opening of the oxirane ring under the previously reported conditions gave compound **24** in 50% overall yield for the two steps.

For the synthesis of compound **4** the epimerization at C_{11} was carried out by treatment of **24** with LDA at −78 °C and reprotonation of the lactone enolate with NH_4Cl at 0 °C,[26] which afforded **4** in 93% yield. Its NMR spectra were consistent with its structure and confirm the structure of 11β,13-dihydro-1-*epi*-inuviscolide for the natural product isolated from *D. graveolens*.[12]

Finally conversion of **24** into the corresponding *exo*-methylene derivative by Grieco's procedure[24] afforded **5** in 45% overall yield. Its NMR spectra were consistent with this structure and confirm 1-*epi*-inuviscolide as the natural product isolated from *F. crispa*,[13] *A. spectabilis*,[11] and *I. anatolica*[14] as its ^{1}H NMR spectral data were identical to the reported data for the natural product.

In summary, 4α-hydroxy-8,12-guaianolides **3**−**5** were synthesized in enantiomerically pure forms from commercially available santonin (**1**). For the synthesis of these compounds a synthetic sequence has been devised which opens a pathway for the synthesis of natural 8-oxyfunctionalized guaianes and 8,12-guaianolides and related compounds.

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Scheme 3

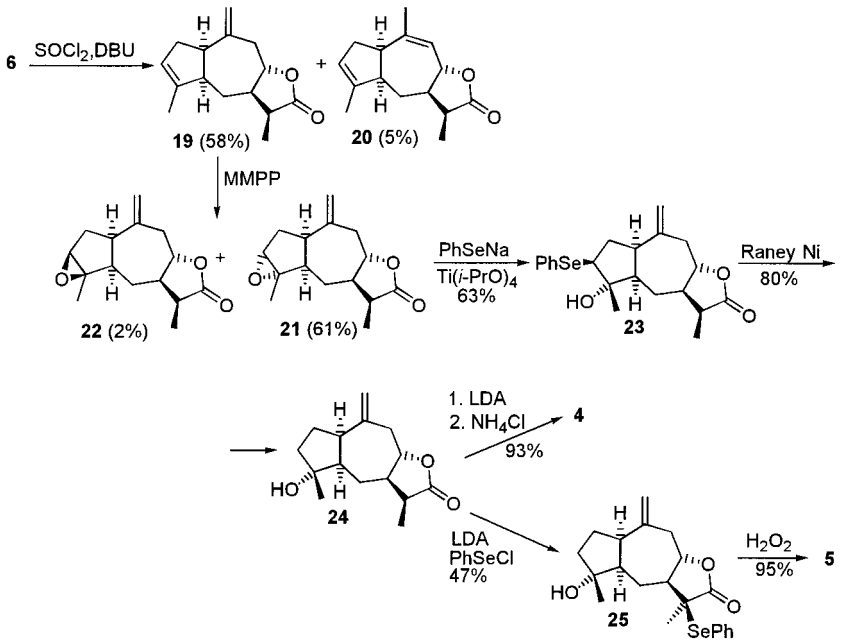

Table 1. ^{13}C NMR Data of Compounds 3−12 (δ, $CDCl_3$)

carbon	3	4	5	6[a]	7	8	9	10	11[a]	12[a]
C_1	124.4[b]	45.6[b]	46.1[b]	51.6	153.8	46.1[b]	50.7	51.4	50.4	52.5
C_2	30.1[c]	26.7[c]	26.6[c]	33.5	127.3	36.7[c]	36.9	36.5	35.1	32.4
C_3	39.6[c]	43.2	42.8	124.4	186.1	207.6	218.6	72.5[b]	76.7	122.4
C_4	80.7	80.4	80.5	141.0	130.6[b]	160.3[d]	44.1[b]	45.7[c]	47.3	143.8
C_5	54.4	53.9[b]	54.0[b]	48.8	151.1[b]	146.0[d]	47.6	44.3[c]	46.3	50.6[b]
C_6	26.9	25.7[c]	25.5[c]	26.3	125.3	124.7	23.4	25.1	23.7	28.2
C_7	50.5	51.5	47.3	44.9	141.8	140.2	43.7[b]	43.5[c]	44.4	43.5
C_8	81.9	84.7	84.7	81.1	68.1	70.5	72.1	72.2[b]	72.3	72.2
C_9	40.4[c]	40.8	40.5	48.7	38.5	42.9[c]	33.4	33.6	33.5	35.1
C_{10}	140.2[b]	144.2	144.0	72.9	39.5	82.3	83.0	84.1	83.8	84.1
C_{11}	139.3	42.3	139.8	40.4	42.1	47.4[b]	42.6	42.9	42.4	42.3[b]
C_{12}	170.2	178.7	170.2	179.9	173.7	173.4	175.0	175.4	175.2	175.2
C_{13}	113.7	12.4	118.9[d]	9.8	15.2	15.8	12.8	11.8	12.5	12.1
C_{14}	23.2	115.4	116.1[d]	24.0	25.7	22.1	26.9	26.3	26.2	26.1
C_{15}	23.2	23.9	23.9	14.7	10.2	8.4	9.1	9.8	13.4	14.9
OCH_3					52.1	52.2	51.4	51.1	51.2	51.2
CH_3CO					170.2	170.1	170.3	170.3	170.4	170.3
						169.9	170.1	170.3	170.3	170.3
CH_3CO					20.8	21.0	22.6	22.6	22.6	22.7
						20.8	21.1	21.0	21.0	21.1

[a] Assignment by heteronuclear ^{1}H−^{13}C NMR correlation. [b−d] These signals may be interchanged within the corresponding spectrum.

Experimental Section

All melting points are uncorrected. Column chromatography was performed on silica gel (SDS, silica gel 40−60 mm). W-2 Raney Ni was prepared according to Mozingo,[27] and deactivated by heating the ethanolic suspension at 60 °C for 3−4 days. IR spectra were recorded as liquid films for oils and as KBr disks for solids. Specific rotations were measured in $CHCl_3$. ^{1}H and ^{13}C NMR were measured in $CDCl_3$; chemical shifts are reported in parts per million and *J* values in hertz. NMR were run at 200.1, 299.95, or 399.95 Mz for ^{1}H and at 50.3, 75.43, or 100.58 MHz for ^{13}C. The carbon type (methyl, methylene, methine, or quaternary) was determined by DEPT experiments. ^{13}C NMR spectral data of compounds **3**−**12** are listed in Table 1 and those of compounds **13**−**25** in Table 2. Mass spectra were run by chemical ionization (with CH_4). Crystal data for **9**: $C_{20}H_{30}O_7$, M = 382.44, monoclinic, $P2_1/m$, a = 8.726(2) Å, b = 12.769(3) Å, c = 9.070(2) Å, β = 90.52(3)°, V = 1010.6(3) Å^3, Z = 2, μ(Mo Kα) = 0.094 mm^{-1}, 1987 reflections collected, θ range 2.25−24.97°, 1861 independent reflections (R_{int} = 0.0165). Final R indices were R1 = 0.0425 and wR2 = 0.0911 [$I > 2\sigma(I)$]. Residual electron densities were 0.285 and −0.162 e Å^{-3}. Data were collected for a crystal of size 0.1 × 0.1 × 0.2 mm at 293 K with a Siemens P-4 diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) and the θ−2θ scan technique. Lorentz-polarization and absorption corrections were applied to the data. The structure was solved by direct methods using SHELX86 and refined by the full-matrix least-squares method on F^2 using SHELXL93.[28] All non-hydrogen atoms were refined anisotropically.

Methyl (*11S*)-8α-Acetoxy-3-oxoeudema-1,4,6-trien-12-oate (7). A mixture of **2**[6] (2.46 g, 8.91 mmol), Ac_2O (24 mL), pyridine (24 mL), and a catalytic amount of DMAP was stirred at rt for 3 h. The reaction was quenched with 2 M HCl and then extracted with EtOAc. The combined organic layers were washed with aqueous $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated. Chromatography of the residue (7:3 hexane/

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Table 2. ^{13}C NMR Data of Compounds 13−25 (δ, $CDCl_3$)

carbon	13	14	15	16[a]	17	18[a]	19	20	21	22	23[a]	24	25
C_1	49.7[b]	39.8[b]	127.4[b]	124.7[b]	124.4[b]	124.6[b]	48.3	48.5[b]	46.9[b]	44.8[b]	46.8[b]	45.1[b]	45.2[b]
C_2	29.2[c]	28.5[c]	33.4	39.4[c]	29.8[c]	29.8[c]	36.3	35.8	32.0	33.3	35.2	26.6	26.7
C_3	63.7	60.9	63.5	53.4[d]	39.6[c]	39.6[c]	124.0	123.3[c]	62.3	64.0	55.7	43.7	43.5
C_4	67.5	65.7	67.0	81.2	80.9	81.0	141.0	137.9	65.9	66.9	80.3	80.2	80.4
C_5	45.8[b]	38.0[b]	51.6	54.8[d]	54.8	54.6	52.4[b]	50.7[b]	50.2[b]	45.8	51.2[b]	53.5[b]	53.9[b]
C_6	22.7[c]	27.4[c]	27.0	25.5	26.1[c]	26.7[c]	24.8	27.2	23.4	22.7	22.7	22.8	23.5
C_7	45.8[b]	47.2[b]	47.9	48.6	49.9	58.8	47.2[b]	43.9	42.8	46.9	42.7	47.0	55.9
C_8	80.6	82.0	79.3	80.8	80.5	79.0	84.7	83.2	84.3	84.0	83.8	84.0	82.4
C_9	50.0	41.4	39.2	40.6[c]	40.1[c]	39.7[c]	42.6	122.6[c]	41.0	40.4	44.4	40.8	40.9
C_{10}	72.9	72.4	140.2[b]	135.7[b]	140.3[b]	140.4[b]	145.2	145.6	145.2	144.1	142.3	140.0	143.7
C_{11}	40.4	40.2	40.4	40.4	40.6	51.0	40.5	40.4	40.6	43.6[b]	40.2	40.3	51.1
C_{12}	179.6	180.2	178.8	179.6	179.4	175.7	179.7	179.8	179.2	179.6	179.5	179.7	176.0
C_{13}	9.5	10.0	10.0	10.4	10.3	22.0	9.5	10.1	9.5	9.6	9.5	9.5	21.9
C_{14}	24.8	33.3	22.3	20.2	23.0	23.0	115.2	27.6	115.7	117.7	115.4	115.2	115.5
C_{15}	15.8	15.6	16.1	23.3	23.5	23.7	14.8	15.1	16.1	16.0	20.7	23.7	23.9

[a] Aromatic carbons: for **16**, δ 127.4, 129.1, 129.6, 133.7; for **18**, δ 124.3, 129.0, 129.7, 138.3; for **23**, δ 127.4, 128.8, 129.1, 133.8; for **25**, δ 124.0, 128.9, 129.7, 138.3. [b −d]These signals may be interchanged within the corresponding spectrum.

EtOAc) gave 2.55 g (90%) of acetate **7**: yellow oil; $[\alpha]^{19}_D$ +271.8 (*c* 1.7); IR (NaCl) 1737, 1648 cm^{-1}; MS *m/e* 319 (M^+ + 1, 72), 318 (M^+, 18), 275 (25), 259 (86), 227 (37) 199 (100); HRMS 318.1456, $C_{18}H_{22}O_5$ required 318.1467; ^{1}H NMR (400 MHz) δ 6.72 (1H, d, *J* = 9.7), 6.70 (1H, br s), 6.25 (1H, d, *J* = 9.7), 5.70 (1H, br dd, *J* = 9.8, 7.9), 3.67 (3H, s), 3.39 (1H, q, *J* = 7.1), 2.32 (1H, dd, *J* = 6.3, 12.2), 2.04 (3H, s), 1.98 (3H, s), 1.49 (1H, dd, *J* = 9.8, 12.2), 1.37 (3H, d, *J* = 7.1), 1.21 (3H, s).

Methyl (*11S*)-8α,10α-Diacetoxy-3-oxo-1α*H*-guaia-4,6-dien-12-oate (8). A solution of acetate **7** (748 mg, 2.35 mmol) in AcOH (75 mL) under argon was irradiated with a 400 W UV lamp for 9 h. Removal of the solvent at reduced pressure afforded an oil which was chromatographed (6:4 hexane/EtOAc) to give 166 mg (22%) of starting material **7** and 479 mg (54%) of guaiane **8**: yellow solid; mp 119−121 °C (hexane−EtOAc); $[\alpha]^{21}_D$ −167.1 (*c* 1.52); IR (KBr) 1738, 1696 cm^{-1}; MS *m/e* 379 (M^+ + 1, 10), 319 (30), 259 (100); HRMS 379.1743 (M^+ + 1), $C_{20}H_{27}O_7$ required 379.1757; ^{1}H NMR (400 MHz) δ 6.59 (1H, s), 5.47 (1H, dd, *J* = 4.1, 6.7), 4.46 (1H, br s), 3.68 (3H, s), 3.46 (1H, q, *J* = 7.0), 2.98 (1H, dd, *J* = 6.7, 15.0), 2.45 (1H, dd, *J* = 5.3, 16.6), 2.38 (1H, d, *J* = 4.0, 16.6), 2.33 (1H, dd, *J* = 4.1, 15.0), 2.07 (3H, s), 1.97 (3H, s), 1.80 (3H, d, *J* = 2.1), 1.36 (3H, d *J* = 7.0), 1.15 (3H, s).

Methyl (*11S*)-8α,10α-Diacetoxy-3-oxo-1,4,5,7α*H*-guaian-12-oate (9). A solution of **8** (1.36 g, 3.60 mmol) in absolute EtOH (38 mL) was hydrogenated over 10% Pd/C (322 mg) for 2 h and 30 min. After this time, the catalyst was removed by filtration through a pad of silica gel, the filtrate concentrated in vacuo, and the residue chromatographed (9:1 to 6:4 hexane/EtOAc) to give 1.01 g (74%) of compound **9**: solid; mp 143−144 °C (hexane−EtOAc); $[\alpha]^{22}_D$ −8.2 (*c* 1.47); IR (KBr) 1729 cm^{-1}; MS *m/e* 323 (M^+ − AcO, 4), 263 (100), 231 (10); HRMS 323.1863, $C_{18}H_{27}O_5$ (M^+ − AcO) required 323.1858; ^{1}H NMR (400 MHz) δ 4.98 (1H, ddd, *J* = 1.2, 5.6, 10.4), 3.62 (3H, s), 2.68 (1H, ddd, *J* = 5.2, 8.4, 12.8), 2.61 (1H, dddd, *J* = 2.0, 5.2, 7.2, 12.8), 2.55 (1H, br d, *J* = 17.0), 2.52 (1H, dq, *J* = 3.2, 7.2), 2.45 (1H, dq, *J* = 6.8, 7.2), 2.35 (1H, td, *J* = 3.2, 10.4), 2.29 (1H, dd, *J* = 8.4, 18.8), 2.03 (3H, s), 1.97 (1H, dd, *J* = 5.6, 17.0), 1.95 (3H, s), 1.89 (1H, dd, *J* = 12.8, 18.8), 1.49 (3H, s), 1.37 (1H, br d), 1.06 (3H, d, *J* = 7.2), 1.00 (3H, d, *J* = 6.8), 0.84 (1H, ddd, *J* = 10.4, 12.8, 15.2).

Methyl (*11S*)-8α,10α-Diacetoxy-3*β*-hydroxy-1,4,5,7α*H*-guaian-12-oate (10) and Methyl (*11S*)-8α,10α-Diacetoxy-3α-hydroxy-1,4,5,7α*H*-guaian-12-oate (11). A solution of **9** (1.01 g, 2.65 mmol) in MeOH (54 mL) was treated with $NaBH_4$ (298 mg, 7.88 mmol) at 0 °C. After 20 min the reaction was quenched with aqueous NH_4Cl. The usual workup and chromatography (8:2 to 5:5 hexane/EtOAc) separated two compounds, *β*-alcohol **10** (570 mg, 56%) and α-alcohol **11** (408 mg, 40%). Data for compound **10**: solid; mp 131−132 °C (hexane−EtOAc); $[\alpha]^{26}_D$ +62.3 (*c* 1.51); IR (KBr) 3580−3560, 1724 cm^{-1}; MS *m/e* 383 (M^+ − 1, 9), 351 (5), 334 (13), 274 (28); HRMS 383.2065, $C_{20}H_{31}O_7$ (M^+ − 1) required 383.2070; ^{1}H NMR (400 MHz) δ 5.00 (1H, br dd, *J* = 6.0, 10.4), 4.14 (1H, br dd, *J* = 6.0, 6.8), 3.65 (3H, s), 2.51 (1H, br d, *J* = 16.4), 2.47−2.55 (1H, m), 2.35−2.20 (3H, m), 2.15 (1H, dd, *J* = 6.0, 16.4), 2.15−2.05 (1H, m) 2,00 (3H, s), 1.97−1.90 (1H, m), 1.95 (3H, s), 1.48 (3H, s), 1.37−1.33 (3H, m), 1.07 (3H, d, *J* = 7.2), 1.01 (3H, d, *J* = 7.2). Data for compound **11**: yellow oil; $[\alpha]^{28}_D$ +34.3 (*c* 1.34); IR (NaCl) 3500−3100, 1729 cm^{-1}; MS *m/e* 383 (M^+ − 1, 10), 351 (6), 334 (14), 274 (29); HRMS 383.2047, $C_{20}H_{31}O_7$ (M^+ − 1) required 383.2070; ^{1}H NMR (400 MHz) δ 4.96 (1H, ddd, *J* = 1.6, 5.6, 9.6), 3.83 (1H, ddd, *J* = 3.4, 8.0, 8.8), 3.64 (3H, s), 2.63 (1H, ddd, *J* = 6.0, 9.2, 11.2), 2.51 (1H, d, *J* = 16.4), 2.52 (1H, dq, *J* = 3.2, 7.6), 2.25 (1H, ddd, *J* = 3.2, 9.6, 10.0), 2.23−2.19 (1H, m), 2.03 (1H, dd, *J* = 5.6, 16.8), 2.00 (3H, s), 2.00−1.95 (1H, m), 1.95 (3H, s), 1.85 (1H, ddd, *J* = 8.8, 11.2, 14.0), 1.63 (1H, ddd, *J* = 3.4, 9.2, 14.0), 1.45 (3H, s), 1.40 (1H, br d, *J* = 14.4), 1.07 (3H, d, *J* = 7.6), 1.03 (3H, d, *J* = 7.2), 0.88 (1H, ddd, *J* = 10.0, 12.4, 14.4).

Methyl (*11S*)-8α,10α-Diacetoxy-1,5,7α*H*-guai-3-en-12-oate (12). From Compound 10. To a 0 °C precooled solution of 3*β*-alcohol **10** (386 mg, 1.01 mmol) and Et_3N (0.85 mL, 6.05 mmol) in CH_2Cl_2 (5.9 mL) and under argon was added MsCl (360 *μ*L, 4.43 mmol), and the resulting mixture was stirred for 3 h. The reaction was quenched with 10% HCl aqueous to acid pH and extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give an oil which according to ^{1}H NMR analysis consisted mainly of the mesyl derivative. A suspension of the oil and Li_2CO_3 (620 mg, 8.40 mmol) in DMF (26 mL) was heated under argon at 100 °C for 2 h. The reaction mixture was cooled, quenched with aqueous saturated NH_4Cl, and extracted with EtOAc. After the usual workup, chromatography (9:1 hexane/EtOAc) gave 178 mg (50%) of **12**: pale yellow oil; $[\alpha]^{26}_D$ +95.5 (*c* 1.57); IR (NaCl) 1735 cm^{-1}; MS *m/e* 307 (M^+ − AcO, 1), 263 (6), 247 (100), 187 (22); HRMS 307.1898, $C_{18}H_{27}O_4$ (M^+ − AcO) required 307.1909; ^{1}H NMR (400 MHz) δ 5.27 (1H, br s), 5.00 (1H, ddd, *J* = 2.8, 5.2, 10.4), 3.65 (3H, s), 2.69 (1H, ddd, *J* = 6.4, 7.2, 8.0), 2.60−2.50 (3H, m), 2.43 (1H, td, *J* = 2.8, 10.4), 2.18 (1H, dd, *J* = 5.2, 16.0), 2.22−2.14 (1H, m), 2.10−2.00 (1H, m), 2.00 (3H, s), 1.96 (3H, s), 1.68 (3H, br s), 1.50 (3H, s), 1.50−1.54 (1H, m), 1.15−1.04 (1H, m), 1.07 (3H, d, *J* = 6.8).

From Compound 11. To a solution of 3α-alcohol **11** (67 mg, 0.173 mmol) and pyridine (0.14 mL, 1.73 mmol) in benzene (1.7 mL) at rt and under argon was added $POCl_3$ (39 *μ*L, 0.415 mmol), and the mixture was heated at reflux for 35 min. After this time, the mixture was cooled at rt, quenched with aqueous NH_4Cl, and extracted with EtOAc. Usual workup afforded an oil which by ^{1}H NMR analysis consisted of a mixture of two epimeric chlorides.

A suspension of this oil, LiBr (30 mg, 0.343 mmol), and Li_2CO_3 (38 mg, 0.510 mmol) in DMF (2 mL) was heated under argon at 100 °C for 2 h and 15 min. The reaction mixture was cooled at rt, quenched with aqueous saturated NH_4Cl, and extracted with EtOAc. After the usual workup, chromatogra-

phy (9:1 hexane/EtOAc) afforded 50 mg (80%) of compound **12** with features identical to those of the compound obtained from **10**.

10α-Hydroxy-1,5,7,11α*H*,8*βH*-guai-3-en-8,12-olide (6). Compound **12** (637 mg, 1.74 mmol) was added to a solution of KOH (2.9 g, 52.2 mmol) in MeOH (13.9 mL), and the mixture was stirred at rt for 2 h. Addition of a 2 M HCl solution to acid pH and usual workup and chromatography (6:4 hexane/EtOAc) afforded 426 mg (98%) of guaianolide **6**: solid; mp 114−117 °C (hexane−EtOAc); $[\alpha]^{27}_D$ −65.1 (*c* 1.66); IR (KBr) 3350−3320, 1766 cm^{-1}; MS *m/e* 251 ($M^+ + 1$, 2), 233 (100); HRMS 251.1637, $C_{15}H_{23}O_3$ ($M^+ + 1$) required 251.1647); ^{1}H NMR (400 MHz) δ 5.34 (1H, br s), 4.15 (1H, ddd, J = 4.4, 10.8, 12.4), 2.90 (1H, br ddd, J = 6.4, 9.2, 9.6), 2.66 (1H, quint, J = 7.6), 2.56 (1H, ddd, J = 3.2, 8.8, 9.2), 2.51 (1H, ddquint, J = 2.4, 3.2, 16.8), 2.43 (1H, dd, J = 4.4, 12.4), 2.45−2.35 (1H, m), 2.29 (1H, td, J = 7.6, 10.8), 1.98 (1H, dd, J = 6.6, 13.6), 1.81 (1H, t, J = 12.4), 1.62 (3H, br s), 1.23 (1H, ddd, J = 9.6, 10.8, 13.6), 1.16 (3H, d, J = 7.6), 1.12 (3H, s).

3*β*,4*β*-Epoxy-10α-hydroxy-1,5,7,11α*H*,8*βH*-guaian-8,12-olide (13) and 3α,4α-Epoxy-10α-hydroxy-7,11α*H*,8*βH*-guaian-8,12-olide (14). To a solution of compound **6** (101 mg, 0.404 mmol) in MeOH (2.6 mL) was added MMPP (238 mg, 0.485 mmol), and the mixture was stirred at rt for 5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2, and the organic layers were washed with aqueous 10% $Na_2S_2O_3$ and brine and dried over Na_2SO_4. After the usual workup and chromatography (6:4 to 4:5 hexane/EtOAc), 37 mg (34%) of compound **13** and 57 mg (53%) of compound **14** were isolated. Data for compound **13**: solid; mp 119−121 °C (hexane−EtOAc); $[\alpha]^{20}_D$ −87.4 (*c* 1.83); IR (KBr) 3500, 1765, 1200 cm^{-1}; MS *m/e* 267 ($M^+ + 1$, 17), 249 (99), 231 (96), 203 (100), 191 (56), 189 (46); HRMS 267.1597, $C_{15}H_{23}O_4$ ($M^+ + 1$) required 267.1596; ^{1}H NMR (300 MHz) δ 4.15 (1H, ddd, J = 3.6, 10.8, 12.0), 3.22 (1H, d, J = 1.5), 2.66 (1H, quint, J = 7.8), 2.46−2.34 (3H, m), 2.27 (1H, dd, J = 1.5, 15.6), 2.10 (1H, ddd, J = 7.8, 10.2, 10.8), 1.97 (1H, ddd, J = 1.5, 10.2, 15.6), 1.90 (1H, br dd, J = 3.9, 13.8), 1.72 (1H, t, J = 12.0), 1.46 (1H, dt, J = 10.2, 13.8), 1.35 (3H, s), 1.19 (3H, s), 1.17 (3H, d, J = 7.8). Data for compound **14**: solid; mp 131−132 °C (hexane−EtOAc); $[\alpha]^{20}_D$ −14.7 (*c* 1.63); IR (KBr) 3479, 1756, 1212 cm^{-1}; MS *m/e* 267 ($M^+ + 1$, 10), 249 (100), 231 (65), 203 (29), 189 (19); HRMS 267.1598, $C_{15}H_{23}O_4$ ($M^+ + 1$) required 267.1596; ^{1}H NMR (400 MHz) δ 4.24 (1H, dt, J = 8.4, 10.8), 3.29 (1H, br s), 3.25 (1H, dddd, J = 1.2, 8.4, 10.8, 13.6), 2.66 (1H, dq, J = 7.6, 8.4), 2.38 (1H, ddd, J = 5.6, 6.4, 11.6), 2.31 (1H, dd, J = 8.4, 15.6), 2.21 (1H, ddd, J = 6.4, 6.8, 12.0), 2.00 (1H, dd, J = 6.8, 13.6), 1.94 (1H, dd, J = 8.4, 15.6), 1.90 (1H, ddd, J = 1.2, 5.6, 12.0), 1.42 (3H, s), 1.35 (1H dd, J = 12.0, 13.6), 1.28 (3H, s), 1.15 (3H, d, J = 7.6), 1.05 (1H, dt, J = 11.6, 13.6).

3α,4α-Epoxy-5,7,11α*H*,8*βH*-guai-1(10)-en-8,12-olide (15). To a solution of compound **14** (64 mg, 0.241 mmol) and pyridine (0.21 mL, 2.487 mmol) in CH_2Cl_2 (5.5 mL) at 0 °C and under argon was added via syringe triflic anhydride (Tf_2O) (127 μL, 0.747 mmol), and the mixture was stirred at rt for 29 h. Additional portions of 0 °C precooled pyridine (0.1 mL) and Tf_2O (64 μL, 0.374 mmol) were added at 5, 8, and 23 h of reaction time. The reaction was quenched with aqueous saturated $NaHCO_3$, and after usual workup (CH_2Cl_2) and chromatography (8:2 to 4:6 hexane/EtOAc) 39 mg (66%) of compound **15** was isolated: solid; mp 60−62 °C (hexane−EtOAc); $[\alpha]^{20}_D$ −46.7 (*c* 1.59); IR (KBr) 1772, 1203 cm^{-1}; MS *m/e* 249 ($M^+ + 1$, 100), 248 (M^+, 23), 231 (32), 220 (14), 203 (17); HRMS 248.1418, $C_{15}H_{20}O_3$ required 248.1412; ^{1}H NMR (400 MHz) δ 3.87 (1H, td, J = 2.4, 10.4), 3.39 (1H, br s), 2.70 (1H, quint, J = 7.6), 2.67 (1H, br d, J = 16.4), 2.63 (1H, br d, J = 12.4), 2.51 (1H, br dd, J = 10.4, 14.0), 2.43 (1H, br d, J = 16.4), 2.42 (1H, dd, J = 2.4, 14.0), 2.31 (1H, dddd, J = 2.8, 7.6, 10.4, 12.4), 1.78 (1H, ddd, J = 2.0, 2.8, 12.4), 1.68 (3H, br s), 1.44 (3H, s) 1.25−1.12 (1H, m), 1.14 (3H, d, J = 7.6).

3*β*-Phenylselenyl-4α-hydroxy-5,7,11α*H*,8*βH*-guai-1(10)-en-8,12-olide (16). $NaBH_4$ (36 mg, 0.962 mmol) was added in portions to a solution of PhSeSePh (272 mg, 0.870 mmol) in DMF (2.2 mL) under Ar at rt, and the mixture was stirred till no evolution of H_2 was observed (75 min). To this solution were added via syringe AcOH (25 μL, 0.440 mmol), compound **15** (56 mg, 0.224 mmol) in DMF (3.6 mL), and Ti(*i*-PrO)$_4$ (140 μL, 0.539 mmol), and the mixture was stirred for 7 h. After this time, the reaction was quenched with water and extracted with EtOAc. Usual workup and chromatography (7:3 hexane/EtOAc) yielded hydroxy selenide **16** (68 mg, 81%): yellow oil; IR (NaCl) 3600−3200, 3057, 1764 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.60−7.50 (2H, m), 7.40−7.30 (3H, m), 3.99 (1H, td, J = 3.0, 10.5), 3.42 (1H, dd, J = 7.8, 12.3), 2.86 (1H, dd, J = 7.5, 15.0), 2.68 (1H, quint, J = 7.8), 2.59 (1H, dd, J = 3.0, 14.1), 2.45−2.25 (3H, m), 2.13 (1H, ddd, J = 2.4, 7.8, 10.5, 12.0), 1.91 (1H, dt, J = 2.4, 12.6), 1.68 (3H, s), 1.17 (3H, s), 1.16 (3H, d, J = 7.8), 1.20−1.10 (1H, m).

4α-Hydroxy-5,7,11α*H*,8*βH*-guai-1(10)-en-8,12-olide (17). Hydroxy selenide **16** (18 mg, 0.044 mmol) in MeOH (5 mL) was treated with deactivated ethanolic W-2 Raney Ni[27] (1 mL, ca. 750 mg) at rt. After 1 h the mixture was filtered through a short plug of silica gel with EtOAc to remove the catalyst and to yield compound **17** (11 mg, 95%): solid; mp 91−94 °C; $[\alpha]^{20}_D$ −53.3 (*c* 1.05); IR (KBr) 3520−3300, 1765 cm^{-1}; MS *m/e* 250 (M^+, 90), 235 (25), 232 (100); HRMS 250.1571, $C_{15}H_{23}O_4$ required 250.1569; ^{1}H NMR (400 MHz) δ 3.98 (1H, td, J = 3.2, 10.4), 2.70 (1H, quint, J = 7.6), 2.56 (1H, dd, J = 3.2, 14.4), 2.52−2.42 (1H, m), 2.48 (1H, br dd, J = 10.8, 14.4), 2.28 (1H, br d, J = 12.0), 2.27−2.17 (1H, m), 2.22 (1H, dddd, J = 2.4, 7.6, 10.8, 12.0), 1.81 (1H, dt, J = 2.4, 12.8), 1.73 (3H, br s), 1.73−1.68 (2H, m), 1.22 (3H, s), 1.16 (3H, d, J = 7.6), 1.05 (1H, q, J = 12.0).

11*β*-Phenylselenyl-4α-hydroxy-5,7α*H*,8*βH*-guai-1(10)-en-8,12-olide (18). To a solution of LDA prepared from *i*-Pr$_2$-NH (31 μL, 0.226 mmol), THF (0.3 mL), and 1.6 M *n*-BuLi in hexane (139 μL, 0.219 mmol) at −78 °C under argon was added via syringe a solution of compound **17** (16 mg, 0.062 mmol) in THF (0.3 mL). The mixture was stirred at −78 °C for 1 h, and then a solution of PhSeCl (44 mg, 0.219 mmol) in THF (0.6 mL) and HMPA (36 μL) was added. The mixture was stirred for an additional 1 h and 30 min at −78 °C, and then the temperature was allowed to rise to −30 °C. After 2 h at this temperature the reaction was quenched with 0.85 mL of aqueous 9% HCl and extracted with EtOAc. Usual workup and chromatography (7:3 to 5:5 hexane/EtOAc) afforded 3.4 mg (21%) of starting material **17** and 14 mg (56%) of phenylselenolactone **18**: yellow solid; mp 170−172 °C (hexane−EtOAc); IR (KBr) 3489, 3060, 1745 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.59 (2H, d, J = 7.4), 7.45−7.25 (3H, m), 4.20 (1H, td, J = 3.3, 9.9), 2.56 (1H, dd, J = 3.3, 14.0), 1.74 (3H, br s), 1.52 (3H, s), 1.27 (3H, s).

4α-Hydroxy-5,7α*H*,8*βH*-guai-1(10),11(13)-dien-8,12-olide (3). To a 0 °C precooled solution of phenylselenolactone **18** (20 mg, 0.048 mmol) in THF (0.5 mL) was added 30% H_2O_2 (12 μL), and the mixture was stirred at 0 °C for 10 min and then at rt for 30 min. The reaction was quenched with brine and extracted with EtOAc, and after usual workup the oil obtained was chromatographed (7:3 to 5:5 hexane/EtOAc) to give 9 mg (74%) of compound **3**: white solid; mp 88−92 °C (hexane−EtOAc); $[\alpha]^{24}_D$ −7.6 (*c* 1.29); IR (KBr) 3590−3196, 1765 cm^{-1}; MS *m/e* 249 ($M^+ + 1$, 67), 248 (M^+, 36), 231 (100), 203 (50); HRMS 248.1411, $C_{15}H_{20}O_2$ required 248.1412; ^{1}H NMR (400 MHz) δ 6.16 (1H, d, J = 3.6), 5.48 (1H, d, J = 2.8), 3.78 (1H, td, J = 3.6, 10.4), 2.65−2.52 (3H, m), 2.48−2.44 (1H, m), 2.35 (1H, br d, J = 11.6), 2.22−2.18 (2H, m), 1.74 (3H, br s), 1.66−1.58 (2H, m), 1.21 (3H, s), 1.10 (1H, br q, J = 12.0).

1,5,7,11α*H*,8*βH*-Guai-3,10(14)-dien-8,12-olide (19) and 7,11α*H*,8*βH*-Guai-3,9(10)-dien-8,12-olide (20). To a −60 °C precooled solution of **6** (200 mg, 0.75 mmol) in THF (1.6 mL) under Ar were added 0.72 mL (4.66 mmol) of DBU and 0.79 mL (10.30 mmol) of $SOCl_2$. After being stirred at this temperature for 18 min, the reaction was quenched with a precooled mixture of ether and water and extracted with ether, and the combined organic layers were washed with Na_2CO_3 and brine. Chromatography of the resulting oil (1:0 to 7:3 hexane/EtOAc) yielded 108 mg (58%) of compound **19** and 9.5 mg (5%) of its isomer **20**. Data for compound **19**: white solid; mp 86−88 °C (hexane−ether); $[\alpha]^{19}_D$ −19.5 (*c* 1.23); IR (KBr) 1769 cm^{-1};

MS *m/e* 233 ($M^+ + 1$, 100), 232 (M^+, 35), 187 (19), 159 (57); HRMS 232.1475, $C_{15}H_{20}O_2$ required 232.1463; ^{1}H NMR (400 MHz) δ 5.38 (1H, br s), 5.02 (1H, s), 4.91 (1H, s), 3.95 (1H, ddd, J = 3.6, 10.8, 11.2), 3.08 (1H, ddd, J = 6.0, 8.4, 9.2), 2.98 (1H, dd, J = 3.6, 11.6), 2.71 (1H, ddd, J = 3.6, 9.2, 11.6), 2.66 (1H, quint, J = 7.6), 2.49 (1H, ddq, J = 1.6, 8.4, 16.0), 2.34 (1H, ddq, J = 2.0, 6.0, 16.0), 2.21 (1H, dd, J = 10.2, 11.6), 2.18 (1H, br ddd, J = 7.6, 10.8, 13.6), 1.71 (1H, ddd, J = 1.2, 3.6, 11.2), 1.65 (3H, br s), 1.13 (3H, d, J = 7.6), 1.02 (1H, ddd, J = 11.2, 11.6, 13.6). Data for compound **20**: white solid; mp 54−56 °C (hexane−ether); $[\alpha]^{18}_D$ −41.8 (*c* 0.91); IR (KBr) 1775, 1646 cm^{-1}; MS *m/e* 233 ($M^+ + 1$, 100), 232 (M^+, 12), 178 (48), 159 (53); HRMS 232.1451, $C_{15}H_{20}O_2$ required 232.1463; ^{1}H NMR (400 MHz) δ 5.74 (1H, s), 5.37 (1H, s), 4.66 (1H, br d, J = 10.4), 2.78 (1H, dt, J = 7.2, 11.6), 2.67 (1H, dq, J = 7.6, 8.0), 2.47 (1H, br dd, J = 7.2, 14.4), 2.29 (1H, ddd, J = 4.4, 7.2, 14.8), 2.17 (1H, ddd, J = 8.0, 10.4), 2.04 (1H, br dd, J = 11.6, 14.4), 1.97 (1H, dd, J = 4.4, 13.8), 1.81 (3H, s), 1.72 (3H, s), 1.25−1.10 (1H, m), 1.17 (3H, d, J = 8.0).

3α,4α-Epoxy-1,5,7,11α*H*,8*βH*-guai-10(14)-en-8,12-olide (21) and 3*β*,4*β*-Epoxy-1,5,7,11α*H*,8*βH*-guai-10(14)-en-8,12-olide (22). To a 0 °C precooled solution of compound **19** (94 mg, 0.40 mmol) in MeOH (2.58 mL) was added MMPP (239 mg, 0.48 mmol). The mixture was stirred at this temperature for 24 h, and additional portions of MMPP (15−20 mg) were added at 19 and 21 h. After usual workup the solid obtained was purified by chromatography (9:1 to 7:3 hexane/EtOAc) to separate *β*-epoxide **22** (2 mg, 2%) and α-epoxide **21** (61 mg, 61%). Data for compound **21**: solid; mp 51−53 °C (hexane−EtOAc); $[\alpha]^{20}_D$ −74.9 (*c* 0.94); IR (NaCl) 1775, 1199 cm^{-1}; MS *m/e* 249 ($M^+ + 1$, 100), 248 (M^+, 15), 231 (58), 203 (32); HRMS 248.1403, $C_{15}H_{20}O_3$ required 248.1412; ^{1}H NMR (400 MHz) δ 4.98 (1H, br d, J = 1.6), 4.89 (1H, br d, J = 2.0), 3.89 (1H, td, J = 2.8, 10.4), 3.31 (1H, s), 2.94 (1H, dd, J = 2.8, 11.6), 2.81 (1H, br dt, J = 7.6, 10.4), 2.68 (1H, quint, J = 7.6), 2.30−2.25 (2H, m), 2.25 (1H, br t, J = 11.6), 2.16 (1H, ddt, J = 1.6, 7.6, 11.6), 1.68 (1H, dd, J = 12.4, 12.6), 1.67 (1H, br d, J = 13.6), 1.45 (3H, s), 1.13 (3H, d, J = 7.6), 1.00 (1H, dt, J = 11.6, 13.6). Data for compound **22**: oil; IR (NaCl) 1770, 1200 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.13 (1H, s), 5.11 (1H, s), 3.99 (1H, td, J = 5.0, 11.2), 3.32 (1H, s), 2.99 (1H, dd, J = 5.0, 11.2), 2.73 (1H, br dd, J = 9.6, 10.4), 2.66 (1H, quint, J = 7.6), 2.32 (1H, ddd, J = 5.6, 9.6, 12.4), 2.25 (1H, d, J = 15.6), 2.20−2.10 (2H, m), 2.01 (1H, t, J = 11.2), 1.84 (1H, dd, J = 5.6, 13.6), 1.36 (3H, s), 1.30 (1H, ddd, J = 9.6, 10.4, 13.6), 1.17 (3H, d, J = 7.6).

3*β*-Phenylselenyl-4α-hydroxy-1,5,7,11α*H*,8*βH*-guai-10(14)-en-8,12-olide (23). $NaBH_4$ (20 mg, 0.529 mmol) was added in portions to a solution of PhSeSePh (149 mg, 0.477 mmol) in DMF (1.2 mL) under Ar at rt for 75 min. To the resulting mixture were added via syringe AcOH (13 μL, 0.230 mmol), compound **21** (30 mg, 0.122 mmol) in DMF (2 mL), and Ti(*i*-PrO)$_4$ (80 μL, 0.308 mmol), and the mixture was stirred for 32 h with addition of additional portions of Ti(*i*-PrO)$_4$ (40 μL, 0.15 mmol) at 15, 22, and 29 h. Usual workup and chromatography (8:2 to 5:5 hexane/EtOAc) yielded hydroxy selenide **23** (33 mg, 66%): oil; IR (NaCl) 3570−3310, 3067, 1775 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.65−7.50 (2H, m), 7.35−7.20 (3H, m), 5.10 (1H, br s), 5.02 (1H, br s), 3.91 (1H, ddd, J = 4.4, 10.8, 11.2), 3.46 (1H, dd, J = 7.0, 13.2), 3.05 (1H, dd, J = 4.4, 11.5), 2.82 (1H, br q, J = 9.0), 2.61 (1H, quint, J = 7.8), 2.30−1.90 (5H m), 1.81 (1H, dd, J = 4.4, 13.5), 1.13 (3H, d, J = 7.8), 1.07 (3H, s).

4α-Hydroxy-1,5,7,11α*H*,8*β*H*-guai-10(14)-en-8,12-olide (24). From hydroxy selenide **23** (28 mg, 0.068 mmol) and according to the procedure for the synthesis of **17** was obtained compound **24** (14 mg, 80%): solid; mp 105−107 °C (EtOAc); $[\alpha]^{22}_D$ −94.6 (*c* 1.12); IR (KBr) 3600−3230, 3062, 1777 cm^{-1}; MS *m/e* 250 (M^+, 4), 235 (6), 232 (100), 192 (21); HRMS 250.1565, $C_{15}H_{22}O_3$ required 250.1569; ^{1}H NMR (400 MHz) δ 5.08 (1H, s), 5.02 (1H, s), 3.97 (1H, td, J = 4.4, 11.2), 3.04 (1H, dd, J = 4.4, 11.6), 3.00 (1H, br dd, J = 8.4, 10.4), 2.65 (1H, dq, J = 7.6, 8.0), 2.12 (1H, dd, J = 11.2, 11.6), 2.20−2.08 (2H, m), 1.92−1.80 (1H, m), 1.85−1.60 (4H, m), 1.16 (3H, d J = 8.0), 1.13 (3H, s), 1.02 (1H, ddd, J = 10.8, 12.8, 13.2).

4α-Hydroxy-1,5,7α*H*,8,11*β*H*-guai-10(14)-en-8,12-olide (4). To a solution containing 14 mg (0.058 mmol) of compound **24** in THF (0.4 mL) cooled to −78 °C was added 0.7 mL (0.290 mmol) of a solution of LDA prepared as reported for the synthesis of **18**. The resulting mixture was stirred at −78 °C for 15 min, and then the temperature was allowed to rise to 0 °C. After being stirred for 2 h, the reaction was quenched at 0 °C with an aqueous saturated solution of NH_4Cl. Usual workup yielded 13.4 mg (93%) of compound **4**: colorless oil; $[\alpha]^{20}_D$ +7.1 (*c* 0.85); IR (NaCl) 3650−3150, 3087, 1767 cm^{-1}; MS *m/e* 250 (M^+, 11), 235 (13), 232 (100), 192 (47); HRMS 250.1569, $C_{15}H_{22}O_3$ required 250.1569; ^{1}H NMR (400 MHz) δ 5.07 (1H, s), 5.03 (1H, s), 3.78 (1H, ddd, J = 4.4, 10.8, 11.2), 3.03 (1H, dd, J = 4.4, 12.0), 2.96−3.05 (1H, m), 2.26 (1H, dq, J = 7.2, 11.6), 2.14 (1H, dd, J = 11.2, 12.0), 2.15−2.06 (1H, m), 1.92−1.80 (1H, m), 1.84−1.60 (5H, m), 1.23 (3H, d, J = 7.2), 1.14 (3H, s), 1.07 (1H, ddd, J = 10.8, 12.8, 13.2).

11*β*-Phenylselenyl-4α-hydroxy-1,5,7α*H*,8*βH*-guai-10(14)-en-8,12-olide (25). By the same procedure used in the synthesis of **18**, from compound **24** (17 mg, 0.069 mmol) were obtained 4.4 mg (25%) of starting material **24** and 13 mg (47%) of **25**: pale yellow solid, mp 155−157 °C (hexane−EtOAc); IR (KBr) 3600−3200, 3065, 1768 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.59 (2H, dd, J = 1.7, 8.5), 7.40−7.25 (3H, s), 5.11 (1H, s), 5.04 (1H, s), 4.20 (1H, td, J = 4.6, 10.8), 3.05 (1H, dd, J = 4.6, 11.8), 3.10−2.90 (1H, m), 2.20−2.05 (2H, m), 2.00−1.50 (6H, m), 1.48 (3H, s), 1.19 (3H, s), 1.30−1.10 (1H, m).

4α-Hydroxy-1,5,7α*H*,8*βH*-guai-10(14),11(13)-dien-8,12-olide (5). By the same procedure used in the synthesis of **3**, from phenylselenolactone **25** (11 mg, 0.027 mmol) was obtained 6.5 mg (95%) of **5**: colorless oil; $[\alpha]^{24}_D$ −30.6 (*c* 0.62); IR (NaCl) 3614−3150, 3083, 1765 cm^{-1}; MS *m/e* 249 ($M^+ + 1$, 16), 248 (M^+, 3), 231 (100), 213 (22), 203 (17); HRMS 249.1490, $C_{15}H_{21}O_3$ required 249.1491; ^{1}H NMR (400 MHz) δ 6.19 (1H, d, J = 3.2), 5.50 (1H, d, J = 3.2), 5.07 (2H, br s), 3.82 (1H, ddd, J = 4.8, 10.4, 11.6), 3.15−3.05 (1H, m), 3.08 (1H, dd, J = 4.8, 12.0), 2.62 (1H, ddt, J = 3.2, 10.0, 10.4), 2.28 (1H, dd, J = 11.6, 12.0), 2.17 (1H, ddd, J = 5.2, 10.0, 13.2), 2.06 (1H, dd, J = 5.2, 14.0), 1.94−1.66 (4H, m), 1.19 (3H, s), 1.10 (1H, ddd, J = 10.0, 13.2, 14.0).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **3**−**25** and details of the X-ray data for compound **9** with a labeled ORTEP diagram. This material is available free of charge via the Internet at http://pubs.acs.org.

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