Stereoselective Synthesis of 7,11-Guaien-8,12-olides from Santonin. Synthesis of Podoandin and (+)-Zedolactone A

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Received June 19, 2000

Photochemical rearrangement of hydroxy ester **2**, easily obtained from santonin (**1**), afforded butenolide **4**, a good starting material for the synthesis of 7,11-guaien-8,12-olides. Compound **4** has been transformed into compound **10**, which has been used for the synthesis of podoandin (**5**) and (+)-zedolactone A (*ent*-**6**). Regioselective elimination of the acetyl group on C_{10} afforded directly podoandin (**5**). For the synthesis of *ent*-**6,** a hydroxyl group has been regio- and stereoselectively introduced at the 4α-position through the 3α,4α-epoxide **15**. The basic hydrolysis of the 10-acetyl group in compound **18** took place with concomitant intramolecular conjugated addition of the alkoxide to the butenolide moiety to give ether **19**. Cleavage of the 7,10-oxido bridge via the lactone enolate afforded (+)-zedolactone A (*ent*-**6**). This synthesis has allowed for the establishment of the absolute stereochemistry of natural zedolactone A as the enantiomer of our synthetic product.

7,11-En-8,12-olide or 8,12-furan moieties and related functionalities such as 7,11-en-8-hydroxy-8,12-olide and 7(11),8-dien-8,12-olide are present in many natural sesquiterpenoids, mainly eudesmane, eremophilane, or germacrane.[1] Compounds with these kinds of functionalities have considerable biological importance, as many of them have shown antiinflammatory,[2] ichtiotoxic and cytotoxic,[3] seed germination inhibitory,[4] or molluscicidal activities,[4,5] among others. Consequently, efficient synthesis of these compounds is a challenge which has received much attention in the past decades.[6]

In recent years the isolation of sesquiterpenes bearing these functionalities on a guaiane skeleton from natural sources has been the subject of several reports in the literature.[7−9] In contrast, to the best of our knowledge, a synthetic approach to these kinds of compounds have not been reported in the literature, so far. This fact has aroused our interest and, as a continuation of our research program on the synthesis of biologically active sesquiterpenoids,[10−12] we present in this paper an efficient approach to 7,11-guaien-8,12-olides starting from santonin (**1**) and its application to the synthesis of two 7,11-guaien-8,12-olides, **5** and *ent*-**6**. Structure **5** was reported for a sesquiterpene lactone isolated from *Podocarpus andina*, which has shown molluscicidal activity against the aquatic snail *Biomphalaria glabratus* and inhibits the germination of lettuce seedlings (*Lactuca sativa*).[7] Structure **6** was reported for zedolactone A, a sesquiterpene lactone isolated from the dry rhizomes of *Curcuma aeruginosa*, 'Gajutsu' in Japan, which are used in traditional oriental medicine as a gastrointestinal remedy.[8] This synthesis has allowed for the determination of the absolute stereochemistry of natural zedolactone A as the enantiomer of our synthetic product.

Results and Discussion

We have recently described the synthesis of three 8,12-guaianolides[10] from alcohol **2**, readily obtained from santonin (**1**),[13] in which photochemical rearrangement from the eudesmane to the guaiane framework was achieved by irradiation of the dienone moiety in the 8-acetyl derivative of compound **2**.[10] It is remarkable that the C_6-C_7 double bond does not interfere in this rearrangement. On the other hand, we have also described

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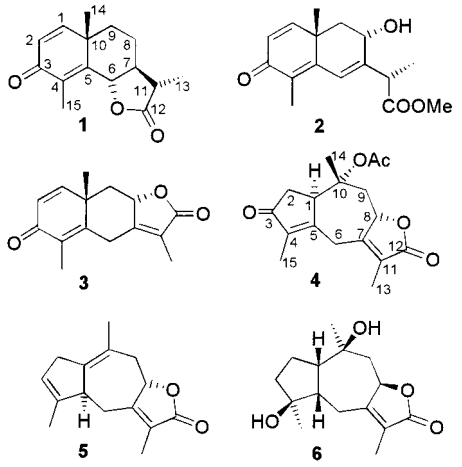
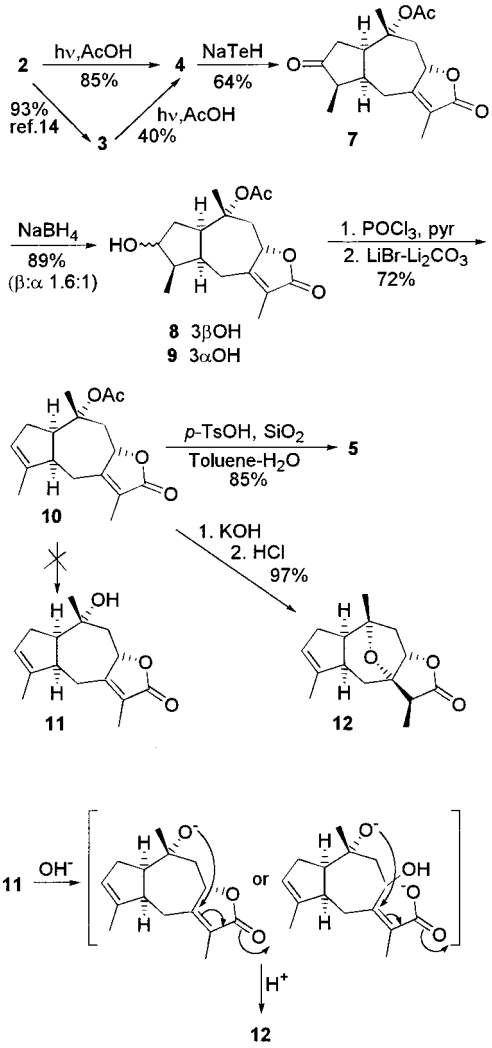
10.1021/jo000927h CCC: $19.00
Published on Web 09/09/2000



that, by treatment in acidic medium (*p*-TsOH/benzene), compound **2** undergoes lactonization with concomitant migration of the C_6-C_7 double bond to the C_7-C_{11} position, affording 7,11-eudesmen-8,12-olide **3** in 93% yield.[14] With these two ideas in mind we thought that compound **4** could be prepared directly from **2**. Since the photochemical rearrangement[15] is carried out in AcOH as solvent and the lactonization to butenolide moiety is catalyzed by acid, we expected that both of these steps could take place in a one-pot conversion during the irradiation. This supposition proved to be correct, and irradiation of compound **2** for 9 h in AcOH afforded directly the 7,11-guaien-8,12-olide **4** in 85% yield (Scheme 1). It is worth remarking that this good result stood in contrast to the low yield (40%) that was obtained upon irradiation of **3** in AcOH.

With compound **4** in our hands we undertook the modification of the A ring functionalization in order to obtain **10**. From this compound we expected to prepare podoandin (**5**) by regioselective elimination of the C_{10}-acetate group, while (+)-zedolactone A (**6**) could be obtained by acetate hydrolysis followed by introduction of a hydroxyl group at C_4. The synthesis of **10** from **4** could be carried out by reduction of the enone to a saturated ketone, reduction of the carbonyl group, and regioselective elimination of the resulting alcohols. In the first instance, reduction of the enone to the ketone was attempted by hydrogenation on 5% Pd/C in acetone since we have observed in a previous work that the C_7-C_{11} double bond is not affected under these conditions.[14] However, compound **4** showed a great resistance to hydrogenation and was recovered unaltered. Fortunately, a repetitive treatment of **4** with NaTeH[16] gave saturated ketone **7** in 64% yield. The positive NOE effects between H_1-H_4, $H_{15}-H_{6\alpha}$ and $H_8-H_{6\beta}$ confirmed the stereochemistry as depicted in Scheme 1. A small amount of a tetrahydro derivative (8%) and 20% of starting material were also isolated from the reaction mixture. Next, treatment of **7** with $NaBH_4$ afforded the two epimeric alcohols **8** (55%) and **9** (34%), whose elimination was carried out by treatment with $POCl_3$ in the presence of pyridine, followed by elimination of the mixture of

Scheme 1



chlorides with Li_2CO_3–LiBr. This afforded regioselectively compound **10** in 72% yield. From this compound, by treatment with *p*-TsOH adsorbed on silica gel in toluene–H_2O[17] at room temperature for 24 h, compound **5** was obtained in 84% yield (Scheme 1). Its NMR spectra were consistent with this structure and agreed with the reported data for podoandin.[7]

For the synthesis of compound *ent*-**6**, the hydrolysis of the acetate group was required. In contrast to the easiness of the acetate elimination, its transformation into an alcohol was troublesome. Under the usual hydrolytic conditions, consisting of treatment with 5%KOH/EtOH followed by aqueous 18% HCl,[10,16] a less polar compound identified as ether **12** was obtained as the main product (57%). This compound was obtained in a nearly quantitative yield (97%), if the reaction was carried out at 0 °C and reprotonated with 9% HCl. The unexpected formation of **12** can be explained by an intramolecular Michael addition of the C_{10}-alkoxide, resulting from the acetate hydrolysis, to the C_7-C_{11} double bond conjugated with the lactone carbonyl group (Scheme 1). Other hydrolytic conditions were also tried without success. Thus LiOH (MeOH–H_2O–THF)[18]

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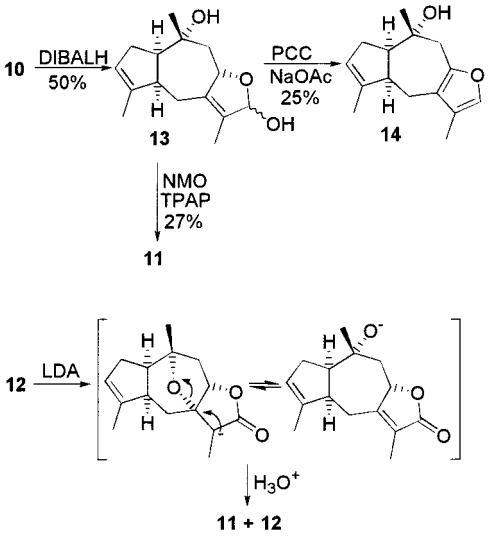
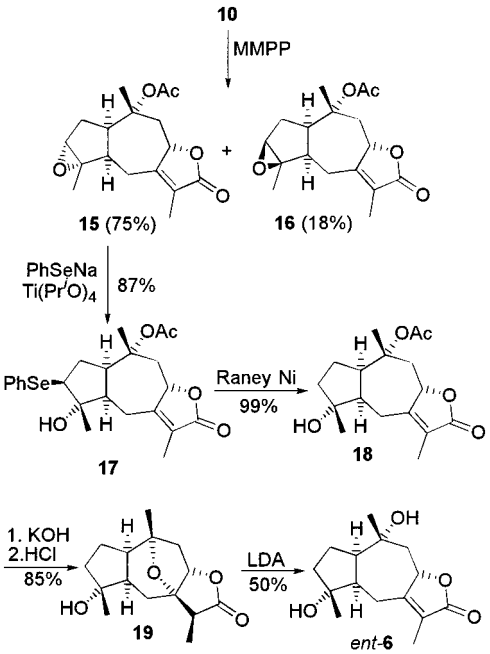
Scheme 2



Scheme 3



afforded **12** (85%), while LiOOH (THF:H_2O, 4:1),[19] DBU in MeOH,[20] 50% NH_3 in MeOH,[21] or 50% Triton B in MeOH[22] also gave epimerized products at C_8. An alternative way was the use of reductive methods (diisobutylaluminum hydride, DIBAL-H)[23] to free the 10-OH. This reagent would also reduce the lactone to lactol, which should be reoxidized in a later step (Scheme 2). Treatment of **10** with DIBAL-H at −45 °C afforded a mixture of lactols **13** with 50% yield; however, reoxidation to the butenolide moiety could not be achieved satisfactorily. Swern reagent[24] gave complex mixtures, while PCC/NaOAc[25] caused dehydration to guaiafurane **14**.[26] Only the use of tetrapropylammonium perruthenate (TPAP) with 4-methylmorpholine *N*-oxide (NMO)[27] allowed compound **11**[28] to be obtained, although in low yield (27%). A last attempt to obtain compound **11** consisted of a retro-Michael reaction[29] on compound **12**. For this purpose compound **12** was treated with LDA (2 equiv) at −78 °C, until disappearance of the starting material. However, after quenching with aqueous HCl the reaction reverted to the starting material, which was recovered (34%) together with compound **11**[28] (50% yield) (Scheme 2).

Since all our attempts to obtain **11** from **10** in good yield failed, we decided to change the order of the reactions, introducing the hydroxyl group on C_4 first and leaving the transformation of the acetate for the last step. To introduce the 4α-OH, we carried out the following sequence. Compound **10** (Scheme 3) was subjected to epoxidation with MMPP[30] to give two stereoisomeric epoxides, **15** (75%) and **16** (18%), whose stereochemistry was deduced by comparison of their spectroscopic data with those of related epoxides[10] and NOE experiments. The α stereochemistry of the oxirane ring in the major epoxide **15** was inferred by the positive NOE found among $H_{6\beta}$ and H_3 and H_8. Cleavage of the oxirane ring by treatment of **15** with PhSeNa/Ti(*i*-PrO)$_4$/DMF[31] gave hydroxyphenylselenide **17** in 87% yield, which by hydrogenolysis of the C−Se bond with deactivated Raney Ni[32] afforded compound **18** in quantitative yield (99%). The transformation of compound **18** into *ent*-**6** required hydrolysis of the C_{10}-acetate group as the last step. On the basis of the results obtained in the hydrolysis of compound **10**, it was also foreseeable that a similar Michael reaction could not be avoided during saponification of the acetate group in compound **18**. Indeed, the basic hydrolysis of **18** afforded ether **19** in 85% yield. Finally, treatment of ether **19** with LDA gave the desired compound *ent*-**6** in 50% yield, together with starting material **19** (45%). The spectral and physical data of synthetic *ent*-**6** were coincident with those described for natural zedolactone A isolated from *C. aeruginosa*.[8] Our synthetic product *ent*-**6** showed an $[\alpha]^{23}_D$ in MeOH of +18.0, whereas the reported value for the natural product was −34.3. Although we do not have an explanation for the difference in the absolute values of the optical rotations, the opposite signs indicates that both products are enantiomers. Because the absolute stereochemistry of our synthetic products is established by unambiguous chemical synthesis from santonin (**1**) whose stereochemistry

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(26) Data for compound **14**: oil; IR (NaCl) 3500−3300, 3040, 1650, 1570 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.02 (1H, s), 5.35 (1H, br s), 2.98 (1H, d, *J* = 16.5), 2.91 (1H, d, *J* = 16.5), 1.90 (3H, d, *J* = 1.5), 1.66 (3H, br s), 1.29 (3H, s).

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(28) Data for compound **11**: oil; IR (NaCl) 3560−3300, 1730 cm^{-1}; ^{1}H NMR (300 MHz) δ 5.39 (1H, br s), 4.95 (1H, br dd, *J* = 5.4, 6.5), 2.92 (1H, dd, *J* = 3.9, 13.8), 2.70−2.60 (1H, m), 2.49 (1H, dd, *J* = 8.4, 15.6), 2.42 (1H, dd, *J* = 6.5, 15.2), 2.30−2.22 (2H, m), 2.07 (1H, dd, *J* = 7.2, 13.8), 2.00 (1H, br dd, *J* = 5.4, 15.2), 1.83 (3H, d, *J* = 2.1), 1.74 (3H, d, *J* = 1.8), 1.27 (3H, s).

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has been established by X-ray analysis,[33] we can conclude that the absolute stereochemistry of natural product isolated from *C. aeruginosa* is (1*S*,4*S*,8*R*,10*S*)-4,10-dihydroxyguai-7(11)-en-8,12-olide.

In summary, an efficient procedure for the preparation of compound **10** from santonin (**1**) has been developed. Compound **10** opens a pathway for the synthesis of natural 7,11-guaien-8,12-olides and compounds with related functionalities. As an example of the usefulness of this method, two 7,11-guaien-8,12-olides, **5** and *ent*-**6,** have been synthesized in enantiomerically pure form, and as a consequence of the synthesis of *ent*-**6**, the absolute stereochemistry of natural zedolactone A has been established.

Experimental Section[34]

10α-Acetoxy-3-oxo-1α*H*,8*βH*-guaia-4,7(11)-dien-8,12-olide (4). A solution of compound **2** (750 mg, 2.71 mmol) in AcOH (30 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 to 4:6 hexanes−EtOAc) to give 700 mg (85%) of compound **4**: solid; mp 162 °C dec (hexanes−EtOAc); $[\alpha]^{25}_D$ +13.6 (*c* 1.03); IR (KBr) 1756, 1727, 1639 cm^{-1}; MS *m/e* 304 (M^+, 2), 262 (66), 244 (100), 215 (26), 204 (16); HRMS 304.1319, $C_{17}H_{20}O_5$ (M^+) required 304.1310; ^{1}H NMR (400 MHz) δ 4.82 (1H, br dd, J = 5.4, 11.6), 3.94−3.86 (1H, m), 3.84 (1H, br d, J = 20.1), 3.50 (1H, br d, J = 20.1), 2.85 (1H, dd, J = 5.4, 12.8), 2.48 (1H, t, J = 12.3), 2.43 (2H, d, J = 4.0), 1.99 (3H, s), 1.88 (3H, t, J = 1.6), 1.77 (3H, br d, J = 1.2), 1.20 (3H, s); ^{13}C NMR (200 MHz) δ 206.1, 172.9, 170.0, 164.3, 157.1, 140.0, 125.6, 82.0 (C), 78.6, 49.5 (CH), 43.9, 37.2, 28.9 (CH_2), 22.1, 19.8, 8.6, 8.3 (CH_3).

10α-Acetoxy-3-oxo-1,5α*H*,8*βH*-guai-7(11)-en-8,12-olide (7). A suspension of tellurium powder (1.60 g, 12.3 mmol) and $NaBH_4$ (1.14 g, 29.5 mmol) in deoxigenated EtOH (33 mL) was refluxed under argon for 1 h. After this time, the resulting deep purple solution was cooled to 0 °C and a solution of 1.8 mL of glacial AcOH in 6.7 mL of EtOH was added, followed by a solution of **4** (934 mg, 3.07 mmol) in 5.5 mL of EtOH and 11 mL of benzene. The resulting mixture was stirred at room temperature for 3 days. After this time, the reaction flask was open to air, water added, and the mixture stirred for 1 h. The reaction mixture was filtered through Celite, washed with brine, dried, and concentrated to give a residue which was subjected to the same reaction conditions. Chromatography of the oil obtained (7:3 to 3:7 hexane/EtOAc) separated starting material **4** (187 mg, 20%), a tetrahydro derivative (75 mg, 8%), and 602 mg (64%) of ketone **7**: solid; mp 120−122 °C (hexanes−EtOAc); $[\alpha]^{25}_D$ +12.3 (*c* 1.46); IR (KBr) 1740, 1724, 1680 cm^{-1}; MS *m/e* 306 (M^+, 0.3), 264 (11), 246 (100), 217 (13); HRMS 306.1463, $C_{17}H_{22}O_5$ (M^+) required 306.1467; ^{1}H NMR (400 MHz) δ 4.96 (1H, br d, J = 7.6), 3.42 (1H, ddd, J = 5.2, 8.4, 13.2), 2.69 (1H, dd, J = 3.6, 13.2), 2.62 (1H, d, J = 16.5), 2.53 (1H, quint, J = 7.2), 2.45−2.35 (1H, m), 2.36 (1H, dd, J = 8.4, 17.2), 2.15 (1H, dd, J = 7.6, 16.5), 2.06 (1H, dd, J = 13.2, 17.2), 1.86 (3H, s), 1.84 (3H, d, J = 2.0), 1.69 (1H, dd, J = 10.4, 13.2), 1.55 (3H, s), 1.12 (3H, d, J = 7.2); ^{13}C NMR (200 MHz) δ 215.5, 174.5, 169.8, 159.3, 123.1, 83.5 (C), 79.9, 50.5, 44.7, 41.1 (CH), 36.6, 32.7 (CH_2), 27.4 (CH_3), 22.4 (CH_2), 21.9, 9.3, 8.0 (CH_3).

10α-Acetoxy-3*β*-hydroxy-1,4,5α *H*,8*βH*-guai-7(11)-en-8,-12-olide (8) and 10α-Acetoxy-3α-hydroxy-1,4,5α*H*,8*βH*-guai-7(11)-en-8,12-olide (9). A solution of **7** (950 mg, 3.10 mmol) in MeOH (63 mL) was treated with $NaBH_4$ (348 mg, 9.12 mmol) at 0 °C. After 20 min the reaction was quenched with aqueous NH_4Cl. The usual workup and chromatography (4:6 to 2:8 hexane/EtOAc) separated compounds **8** (525 mg, 55%) and **9** (325 mg, 34%). Data for compound **8**: solid; mp 118−120 °C (hexanes−EtOAc); $[\alpha]^{21}_D$ +81.6 (*c* 0.98); IR (KBr) 3530−3400, 1735, 1680 cm^{-1}; MS *m/e* 277 ($M^+ + C_2H_5 -$ AcOH, 6), 266 (6), 249 (100), 231 (51), 230 (17); HRMS 277.1807, $C_{17}H_{25}O_3$ ($M^+ + C_2H_5 -$ AcOH) required 277.1803; ^{1}H NMR (250 MHz) δ 4.94 (1H, br d, J = 7.1), 4.22 (1H, td, J = 3.0, 7.2), 2.91 (1H, ddd, J = 4.6, 8.6, 12.9), 2.63 (1H, dd, J = 3.6, 13.2), 2.52 (1H, d, J = 16.6), 2.40−2.20 (2H, m), 2.28 (1H, dd, J = 7.1, 16.6), 2.10−1.90 (1H, m), 1.90−1.75 (2H, m), 1.79 (6H, br s), 1.49 (3H, s), 1.09 (3H, d, J = 7.0); ^{13}C NMR (200 MHz) δ 175.3, 170.1, 161.8, 121.9, 84.6 (C), 80.5, 73.1, 48.6, 43.3 (CH), 36.3, 33.2 (CH_2), 27.4 (CH_3), 23.3 (CH_2), 22.2, 10.1, 8.0 (CH_3). Data for compound **9**: oil; $[\alpha]^{20}_D$ +44.6 (*c* 1.30); IR (NaCl) 3530−3410, 1752, 1736, 1676 cm^{-1}; MS *m/e* 277 ($M^+ + C_2H_5 -$ AcOH, 7), 250 (16), 249 (100), 231 (75), 230 (18); HRMS 277.1804, $C_{17}H_{25}O_3$ ($M^+ + C_2H_5 -$ AcOH) required 277.1803; ^{1}H NMR (250 MHz) δ 4.92 (1H, br d, J = 7.2), 3.96 (1H, ddd, J = 3.3, 6.4, 9.4), 3.25 (1H, ddd, J = 4.0, 8.2, 12.2), 2.66 (1H, dd, J = 2.5, 10.7), 2.55 (1H, d, J = 16.4), 2.20 (1H, dd, J = 7.2, 16.4), 2.10−1.90 (3H, m), 1.80 (6H, br s), 1.90−1.60 (2H, m), 1.49 (3H, s), 1.12 (3H, d, J = 6.5); ^{13}C NMR (200 MHz) δ 174.9, 169.9, 160.9, 122.4, 84.1 (C), 80.3, 77.2, 48.0, 47.5, 44.0 (CH), 35.2, 33.0 (CH_2), 27.0 (CH_3), 22.9 (CH_2), 22.1, 13.9, 8.0 (CH_3).

10α-Acetoxy-1,5α*H*,8*β* H-guaia-3,7(11)-dien-8,12-olide (10). To a solution of the mixture of alcohols obtained in the previous step (755 mg, 2.45 mmol) and pyridine (2.02 mL, 24.90 mmol) in benzene (24.5 mL) at room temperature and under argon was added $POCl_3$ (562 μL, 6.05 mmol), and the solution was heated at reflux for 35 min. After this time, the mixture was cooled to room temperature, quenched with aqueous NH_4Cl, and extracted with EtOAc. Usual workup afforded an oil which was suspended with LiBr (432 mg, 4.90 mmol) and Li_2CO_3 (547 mg, 7.35 mmol) in DMF (28.8 mL), and the suspension was heated under argon at 100 °C for 2 h and 15 min. The reaction mixture was cooled to room temperature, quenched with aqueous saturated NH_4Cl, and extracted with EtOAc. After the usual workup, chromatography (8:2 hexane/EtOAc) afforded 511 mg (72%) of compound **10**: oil; $[\alpha]^{22}_D$ +44.4 (*c* 1.08); IR (NaCl) 1757, 1735, 1690 cm^{-1}; MSEI *m/e* 290 (M^+, 1), 246 (31), 230 (100), 228 (29), 215 (31); HRMS 290.1530, $C_{17}H_{22}O_4$ (M^+) requiered 290.1518; ^{1}H NMR (200 MHz) δ 5.36 (1H, br s), 5.00−4.90 (1H, m), 3.25 (1H, dt, J = 7.9, 10.1), 2.81 (1H, dd, J = 4.0, 13.5), 2.52 (1H, dd, J = 3.6, 16.0), 2.55−2.30 (1H, m), 2.35 (1H, dd, J = 6.6, 16.0), 2.30−2.20 (2H, m), 2.01 (1H, t, J = 13.5), 1.83 (3H, s), 1.81 (3H, s), 1.72 (3H, d, J = 1.2), 1.53 (3H, s); ^{13}C NMR (200 MHz) δ 174.9, 169.9, 160.6, 143.0 (C), 123.7 (CH), 121.7, 84.2 (C), 80.0, 49.7, 47.9 (CH), 35.1, 32.4 (CH_2), 26.8 (CH_3), 26.3 (CH_2), 22.2, 14.9, 8.0 (CH_3).

5α*H*,8*βH*-Guaia-1(10),3,7(11)-trien-8,12-olide (Podoandin, 5). To a solution of compound **10** (29 mg, 0.10 mmol) in water-saturated toluene (2.2 mL) was added previously prepared *p*-TsOH−SiO_2[17] (159 mg). The mixture was stirred at room temperature for 24 h and filtered through silica gel (EtOAc), and the solvent was removed in vacuo to give 19 mg (84%) of **5**: solid: mp 113−114 °C (hexanes−EtOAc); $[\alpha]^{21}_D$ +38.4 (*c* 1.02); IR (KBr) 1745, 1664 cm^{-1}; MS *m/e* 231 (M^+ + 1, 100), 230 (M^+, 31), 229 ($M^+ - 1$, 17), 213 (13); HRMS 230.1316, $C_{15}H_{18}O_2$ (M^+) required 230.1307; ^{1}H NMR (400 MHz) δ 5.49 (1H, br s), 4.55 (1H, br d, J = 12.0), 3.10−2.90 (3H, m), 2.87 (1H, br d, J = 11.6), 2.62 (1H, dd, J = 3.6, 12.8), 2.23 (1H, t, J = 12.8), 1.90−1.70 (1H, m), 1.84 (3H, br s), 1.78 (6H, br s); ^{13}C NMR (200 MHz) δ 174.3, 163.5, 142.9, 140.6 (C), 124.2 (CH), 122.7, 121.3 (C), 79.3, 49.6 (CH), 39.6, 36.8, 31.2 (CH_2), 21.9, 14.9, 8.2 (CH_3).

7α,10α-Epoxy-1,5,11α*H*,8*βH*-guai-3-en-8,12-olide (12). Compound **10** (33 mg, 0.11 mmol) in EtOH (0.5 mL) was added to a solution of 5% aqueous KOH (6.4 mL), and the mixture was stirred at room temperature for 1 h. After diluting with EtOAc and cooling to 0 °C, the reaction was quenched with 9% aqueous HCl and extracted with EtOAc in the usual way. Removal of the solvent afforded 27 mg (97%) of compound **12**: solid; mp 127−129 °C (hexanes−EtOAc); $[\alpha]^{18}_D$ +20.4 (*c* 0.78); IR (KBr) 3034, 1777, 1374 cm^{-1}; MS *m/e* 249 (M^+ + 1, 100), 248 (M^+, 21), 231 (59), 203 (33), 175 (38); HRMS 248.1418,

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(34) For a general description of the experimental procedures employed in this research, see ref 10.

$C_{15}H_{20}O_3$ (M^+) required 248.1412; ^{1}H NMR (400 MHz) δ 5.34 (1H, br s), 4.42 (1H, dd, J = 2.4, 7.2), 2.91−2.85 (1H, m), 2.50−2.40 (1H, m), 2.44 (1H, q, J = 7.6), 2.42 (1H, dd, J = 7.2, 14.0), 2.31 (1H, dd, J = 7.6, 8.4), 2.13 (1H, dd, J = 8.8, 14.4), 1.82 (1H, br d, J = 17.2), 1.77 (1H, d, J = 14.4), 1.71 (3H, br s), 1.52 (1H, ddd, J = 1.2, 2.4, 14.0), 1.29 (3H, s), 1.25 (3H, d, J = 7.6); ^{13}C NMR (200 MHz) δ 177.9, 140.7 (C), 125.2, 85.5 (CH), 85.1, 84.4 (C), 44.2, 44.0, 43.0 (CH), 40.7, 34.1, 28.4 (CH_2), 26.0, 14.9, 8.1 (CH_3).

10α-Acetoxy-3α,4α-epoxy-1,5α*H*,8*βH*-guai-7(11)-en-8,12-olide (15) and 10α -Acetoxy-3*β*,4*β*-epoxy-1,5α*H*,8*βH*-guai-7(11)-en-8,12-olide (16). To a solution of compound **11** (119 mg, 0.41 mmol) in MeOH (3.5 mL) was added MMPP (243 mg, 0.49 mmol), and the mixture was stirred overnight at room temperature. 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. The usual workup and chromatography (5:5 to 3:7 hexane/EtOAc) afforded 92 mg (75%) of compound **15** and 22 mg (18%) of compound **16**. Data for compound **15**: foam; $[\alpha]^{26}_D$ +55.7 (*c* 1.94); IR (KBr) 1737, 1734, 1687 cm^{-1}; MS *m/e* 307 (M^+ + 1, 3), 275 (53), 248 (85), 247 (58), 246 (100), 229 (87); HRMS 307.1545, $C_{17}H_{23}O_5$ (M^+ + 1) required 307.1545; ^{1}H NMR (400 MHz) δ 4.93 (1H, br d, J = 7.2), 3.30 (1H, s), 2.87 (1H, ddd, J = 5.6, 6.8, 12.0), 2.82 (1H, dd, J = 3.2, 13.2), 2.67 (1H, br d, J = 16.4), 2.17 (1H, ddd, J = 3.2, 5.6, 13.2), 2.10 (1H, dd, J = 7.2, 16.4), 2.04 (1H, dd, J = 6.8, 13.6), 1.93 (1H, t, J = 13.2), 1.85 (3H, d, J = 2.0), 1.79 (3H, s), 1.52 (3H, s), 1.50 (3H, s), 1.55−1.49 (1H, m); ^{13}C NMR (200 MHz) δ 174.6, 169.4, 159.1, 122.8, 83.2 (C), 79.9 (CH), 64.5 (C), 60.0, 43.3, 41.9 (CH), 33.4, 28.1 (CH_2), 27.2 (CH_3), 24.7 (CH_2), 22.0, 15.5, 7.9 (CH_3). Data for compound **16**: oil; $[\alpha]^{24}_D$ +14.5 (*c* 1.10); IR (NaCl) 1744, 1736 cm^{-1}; MS *m/e* 307 (M^+ + 1, 6), 248 (39), 247 (100), 246 (39), 229 (39); HRMS 307.1549, $C_{17}H_{23}O_5$ (M^+ + 1) required 307.1545; ^{1}H NMR (200 MHz) δ 4.84 (1H, br dd, J = 6.6, 9.7), 3.35−3.22 (1H, m), 3.28 (1H, s), 2.88−2.76 (2H, m), 2.47−2.36 (2H, m), 2.10−1.95 (3H, m), 1.90 (3H, s), 1.80 (3H, br s), 1.47 (3H, s), 1.43 (3H, s); ^{13}C NMR (200 MHz) δ 174.0, 169.9, 160.8, 122.9, 84.4 (C), 79.3 (CH), 68.9 (C), 64.4, 47.6, 44.3 (CH), 42.9, 29.6, 23.8 (CH_2), 22.9, 22.5, 16.2, 8.1 (CH_3).

10α-Acetoxy-3*β*-phenylselenyl-4α-hydroxy-1,5α*H*,8*βH*-guai-7(11)-en-8,12-olide (17). $NaBH_4$ (39 mg, 1.03 mmol) was added in portions to a solution of PheSeSePh (290 mg, 0.86 mmol) in DMF (2.3 mL) under Ar at room temperature for 2 h. To this solution were added via syringe AcOH (24 μL, 0.42 mmol), compound **15** (77 mg, 0.25 mmol) in DMF (4 mL), and Ti(*i*-PrO)$_4$ (150 μL, 0.48 mmol), and the mixture was stirred for 22 h. After this time, the reaction was quenched with water and extracted with EtOAc. Usual workup and chromatography (5:5 hexane/EtOAc) afforded 6 mg (8%) of **15** and hydroxy selenide **17** (99 mg, 87%): solid; mp 154−155 °C (hexanes−EtOAc); IR (KBr) 3550−3350, 1735, 1684 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.58−7.55 (2H, m), 7.30−7.23 (3H, m), 4.85 (1H, br t, J = 5.2), 3.54 (1H, dd, J = 7.7, 10.7), 3.22 (1H, dt, J = 8.1, 12.2), 2.80 (1H, dd, J = 3.9, 11.7), 2.60 (1H, dd, J = 6.6, 14.5), 2.40−2.20 (4H, m), 1.84 (3H, s), 1.85−1.95 (1H m), 1.80 (3H, d, J = 1.5), 1.50 (3H, s), 1.38 (3H, s); ^{13}C NMR (200 MHz) δ 174.6, 169.9, 160.6 (C), 133.3 (CH), 129.8 (C), 129.1, 127.3 (CH), 123.0, 83.5, 81.9 (C), 79.4, 52.7, 49.0, 45.7 (CH), 39.0, 35.0 (CH_2), 24.4 (CH_3), 24.2 (CH_2), 22.5, 22.2, 7.9 (CH_3).

10α-Acetoxy-4α-hydroxy-1,5α*H*,8*βH*-guai-7(11)-en-8,12-olide (18). Hydroxy selenide **17** (42 mg, 0.09 mmol) in EtOH (0.7 mL) was treated with deactivated ethanolic W-2 Raney Ni[35] (0.9 mL, ca. 0.5 g) at room temperature. After 30 min the mixture was filtered through a short plug of silica gel (EtOAc) to yield compound **18** (28 mg, 99%): solid, mp 165−167 °C (hexanes−EtOAc); $[\alpha]^{26}_D$ +60.8 (*c* 1.25); IR (KBr) 3500−3400, 1730, 1683 cm^{-1}; MS *m/e* 337 (M^+ + C_2H_5, 1), 249 (40), 231 (100), 230 (18); HRMS 337.2011, $C_{17}H_{24}O_5$ (M^+ + C_2H_5 required 337.2015; ^{1}H NMR (400 MHz) δ 4.94 (1H, dt, J = 1.6, 7.2), 3.50 (1H, ddd, J = 3.0, 8.7, 12.3), 2.71 (1H, br d, J = 8.8), 2.62 (1H, br d, J = 16.0), 2.27 (1H, dd, J = 7.2, 16.0), 1.90−1.70 (5H, m), 1.84 (3H, d, J = 2.4), 1.79 (3H, s), 1.53 (3H, s), 1.60−1.45 (1H, m), 1.38 (3H, s); ^{13}C NMR (200 MHz) δ 174.9, 169.9, 160.2, 122.8, 84.1, 81.5 (C), 80.2, 51.1, 48.0 (CH), 37.1, 33.1 (CH_2), 27.2, 25.3 (CH_3), 24.8, 24.0 (CH_2), 22.2, 8.1 (CH_3).

4α-Hydroxy-7α,10α-epoxy-1,5,11α*H*,8*βH*-guaian-8,12-olide (19). From compound **18** (36 mg, 0.115 mmol) and according to the procedure for the synthesis of **12** (reaction time 3 h) was obtained compound **19** (26 mg, 85%): solid; mp 135−136 °C (hexanes−EtOAc); $[\alpha]^{18}_D$ −21.9 (*c* 1.28); IR (KBr) 3345, 1772, 1376 cm^{-1}; MS *m/e* 267 (M^+ + 1, 15), 249 (100), 248 (20), 231 (19), 175 (12); HRMS 267.1591, $C_{15}H_{23}O_4$ (M^+ + 1) required 267.1596; ^{1}H NMR (400 MHz) δ 4.52 (1H, dd, J = 1.6, 6.8), 2.58−2.49 (1H, m), 2.50 (1H, q, J = 7.2), 2.46 (1H, dd, J = 6.8, 15.4), 2.23 (1H, td, J = 3.6, 14.1), 2.20 (1H, q, J = 10.8), 2.00−1.90 (1H, m), 1.80−1.70 (1H, m), 1.66 (1H, br d, J = 15.4), 1.56 (1H, br s), 1.47 (1H, d, J = 10.8), 1.33 (3H, s), 1.26 (3H, d, J = 7.2), 1.25 (3H, s), 1.20−1.15 (2H, m); ^{13}C NMR (200 MHz) δ 177.6, 85.2 (C), 86.9 (CH), 84.0, 80.7 (C), 45.1, 44.4, 44.1 (CH), 41.0, 38.7 (CH_2), 27.7 (CH_3), 27.0, 25.7 (CH_2), 23.5, 7.9 (CH_3).

4α-Hydroxy-7α,10α-epoxy-1,5,11α*H*,8*βH*-guaian-8,12-olide [(+)-Zedolactone A] (*ent*-6). To a solution of LDA prepared from *i*-Pr$_2$NH (0.2 mL, 1.5 mmol), THF (2.5 mL), and 1.6 M *n*-BuLi in hexane (0.94 mL, 1,5 mmol) at −78 °C under argon was added via syringe a solution of compound **19** (11 mg, 0.041 mmol) in THF (0.3 mL). The mixture was stirred at −78 °C for 1 h, and then the reaction was quenched with an aqueous solution of NH_4Cl, the system was opened, and the temperature allowed to rise to room temperature. The usual workup and chromatrography (1:9 hexane/EtOAc) afforded 5 mg (45%) of starting material **19** and 5.5 mg (50%) of compound *ent*-**6**: oil; $[\alpha]^{23}_D$ +18.0 (*c* 0.30, MeOH); IR (NaCl) 3417, 1736, 1677 cm^{-1}; MS *m/e* 267 (M^+ + 1, 100), 249 (56), 231 (89), 177 (35), 107 (22); HRMS 267.1589, $C_{15}H_{23}O_4$ (M^+ + 1) required 267.1596; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (1H, br d, J = 5.0), 2.72 (1H, dd, J = 3.6, 12.4), 2.73−2.69 (1H, m), 2.32 (1H, dd, J = 6.8, 16.0), 2.08 (1H, dd, J = 2.8, 16.0), 1.98 (1H, ddd, J = 3.6, 5.6, 13.6), 1.91−1.75 (3H, m), 1.82 (3H, d, J = 2.0), 1.75−1.69 (1H, m), 1.60 (2H, br s), 1.54−1.45 (1H, m), 1.39 (3H, s), 1.23 (3H, s); ^{1}H NMR (400 MHz, pyridine-d_5) δ 6.01 (1H, br d, J = 8.0), 5.12 (1H, ddd, J = 2.0, 3.1, 7.2), 5.10 (1H, br s), 3.27 (1H, dt, J = 8.0, 11.2), 2.78 (1H, dd, J = 3.7, 12.4), 2.52−2.40 (1H, m), 2.44 (1H, dd, J = 7.2, 15.6), 2.18 (1H, dd, J = 3.1, 15.6), 2.08−1.98 (2H, m), 1.97 (1H, dd, J = 12.4, 13.2), 1.92−1.88 (1H, m), 1.83 (3H, d, J = 2.0), 1.68−1.56 (1H, m), 1.52 (3H, s), 1.33 (3H, s); ^{13}C NMR (250 MHz, $CDCl_3$) δ 175.0, 160.7, 122.9 (C), 81.7 (CH), 80.5, 73.5 (C), 51.6, 51.1 (CH), 37.5, 36.3 (CH_2), 32.0, 25.1 (CH_3), 24.9, 24.6 (CH_2), 8.1 (CH_3); ^{13}C NMR (400 MHz, pyridine-d_5) δ 175.6, 162.5, 122.0 (C), 81.3 (CH), 80.7, 72.5 (C), 52.9, 51.5 (CH), 38.5, 37.9 (CH_2), 31.6 (CH_3), 25.6 (CH_3), 25.3 (CH_2), 25.2, 8.2 (CH_3).

Acknowledgment. Financial support from European Commission (FAIR CT96-1781) and from Direción General de Investigación Científica y Técnica (DGICYT, Grant PB 94-0985) is gratefully acknowledged. One of us (V.B.) is specially thankful to Conselleria de Cultura, Educació i Ciencia (Generalitat Valenciana) for a grant.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **4**−**10**, **12**, and **15**−**19** .This material is available free of charge via the Internet at http://pubs.acs.org.

JO000927H

(35) (a) Mozingo, R. *Organic Syntheses*; Wiley & Sons: New York, 1955; Collect. Vol III, p 181. (b) W-2 Raney Ni was deactivated by heating the ethanolic suspension at 60 °C for 3−4 days.