Stereoselective Synthesis of (+)-11βH,13-Dihydroestafiatin, (+)-11βH,13-Dihydroludartin, (−)-Compressanolide, and (−)-11βH,13-Dihydromicheliolide from Santonin

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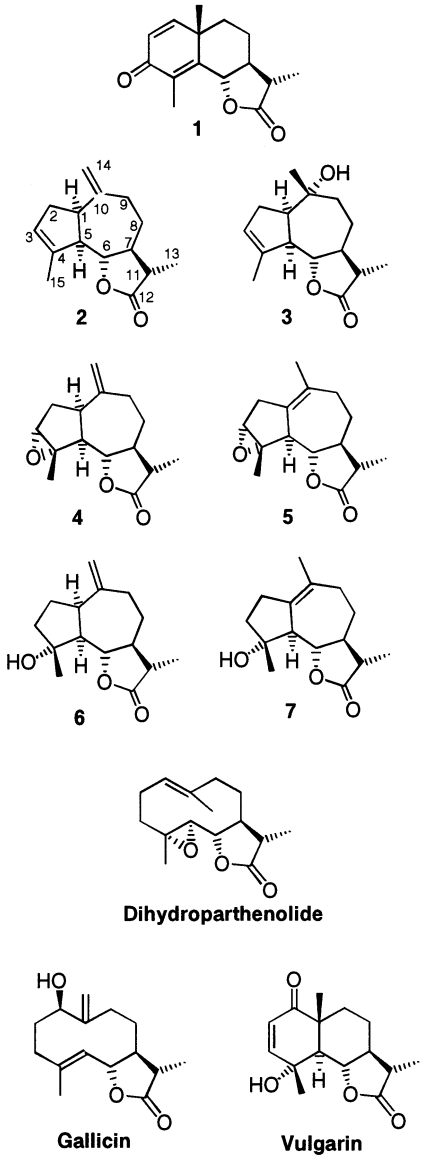
Received March 13, 2002

Starting from **2** and **3**, obtained from santonin (**1**), we have synthesized natural guaianolides **4**−**7**. Chemoselective epoxidation of **2** gave (+)-11βH,13-dihydroestafiatin (**4**), and epoxidation of **3** followed by regioselective elimination of the hydroxyl group afforded (+)-11βH,13-dihydroludartin (**5**). Sharpless' mild regioselective ring-opening of **4** and **5** followed by hydrogenolysis yielded (−)-compressanolide (**6**) and (−)-11βH,13-dihydromicheliolide (**7**), respectively.

The guaianolides represent one of the largest groups of sesquiterpene lactones with over 500 known naturally occurring compounds.[1,2] On account of the wide spectrum of their biological activities[1,2] and their low availability from natural sources, synthetic approaches to the guaianolides have received much attention during the past years.[3,4] However, the total synthesis of the hydroazulene framework with the desired stereochemistry presents many difficulties, and only a few successful total syntheses of guaianolides have been reported in the literature.[3−8] Several short biomimetic syntheses of guaianolides from suitably functionalized natural germacranolides have also been reported in the literature.[1−3] However, this is not an efficient synthetic approach, as either germacranolides are not easily available in sufficient amounts or the reactions afford frequently complex mixtures and poor yields.

Santonin (**1**), a commercially available natural eudesmanolide that possesses a *trans*-6α,12-lactone moiety, constitutes a good starting material for the syntheses of guaianolides.[3,4] In these syntheses the transformation of eudesmane to guaiane skeleton has been carried out through photochemical rearrangement of the cross-conjugated dienone system of santonin[3,4,9] or solvolytic rearrangement of 1β-tosyloxy or 1β-mesyloxy *trans*-decalin derivatives prepared from **1**.[3,4,10] As a continuation of our research program on the synthesis of biologically active sesquiterpenoids, we have carried out the synthesis of several natural guaianolides from santonin (**1**) through photochemical rearrangement.[11−14] In a previous paper[11] we reported a synthesis of guaianolide **2** (isocostus lactone) and **3** from **1** that improved significantly on earlier reports.[15−17] With these compounds as intermediates, a straightforward approach to the synthesis of other 6,12-guaianolides was possible and we report herein the synthesis of (+)-dihydroestafiatin (**4**), (+)-dihydroludartin (**5**), (−)-compressanolide (**6**), and (−)-dihydromicheliolide (**7**).

Dihydroestafiatin (**4**) and dihydroludartin (**5**) are two natural products isolated from *Artemisia adamsii*[18] and *A. carruthii*,[19] respectively. Ando's group has carried out the synthesis of both compounds from santonin (**1**) through a long sequence (14 steps) that afforded **4** and **5** in low yields (1.5% and 0.5%, respectively).[17] Compressanolide (**6**) was first isolated from *Michelia compressa*,[20] and a compound with structure **7** (dihydromicheliolide) was assigned to a natural product named 2,3-dihydrodesacetoxymatricarin that was isolated from *Achillea millefolium* ssp. *collina*.[21] Both **6** and **7** are well-known products of acid cyclization of dihydroparthenolide.[20,22] Compressanolide (**6**) has also been obtained by cyclization of gallicin,[23] and dihydromich-



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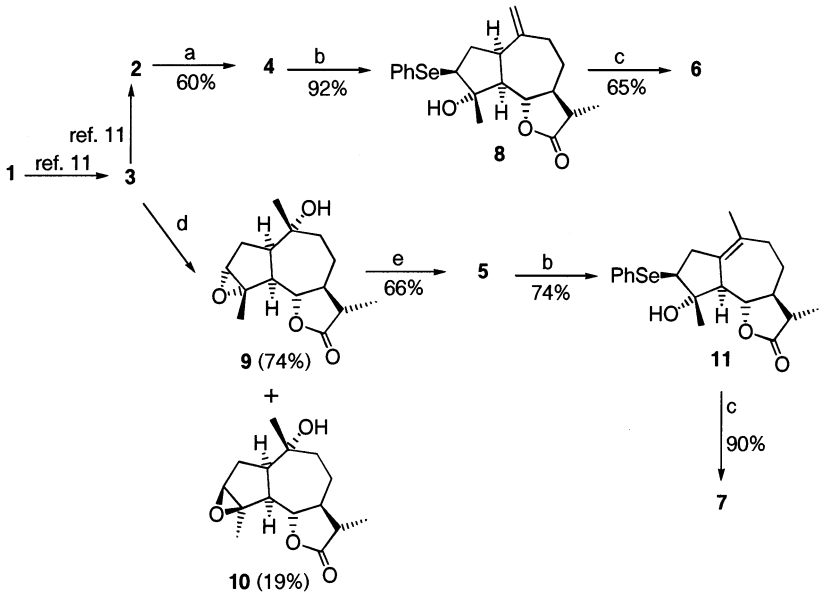
10.1021/np020109f CCC: $22.00 © 2002 American Chemical Society and American Society of Pharmacognosy
Published on Web 09/14/2002

Scheme 1[a]



[a]Reagent and conditions: (a) *m*-CPBA, $CHCl_3$, -10 °C; (b) PhSeNa, Ti(^{i}PrO)$_4$, AcOH, DMF, rt; (c) Raney Ni, EtOH, rt; (d) MMPP, MeOH, rt; (e) Tf_2O, pyridine, CH_2Cl_2, rt.

eliolide (**7**) has been obtained by solvolysis of a 4α-hydroxy-1β-tosyl derivative of vulgarin.[23]

In our approach to the synthesis of (−)-compressanolide (**6**) and (−)-dihydromicheliolide (**7**), the 4α-OH group was introduced by Sharpless' mild regioselective opening of the corresponding 3α,4α-epoxides **4** and **5**, respectively. Isocostus lactone (**2**) was the starting material for the preparation of compounds **4** and **6**. The simplest approach to **4** was the chemo- and stereoselective epoxidation of diene **2**. We have carried out this transformation by treatment of **2** with *m*-chloroperbenzoic acid (*m*-CPBA) at −10 °C, obtaining **4** in 60% yield (6.8% overall yield from santonin). This compound results from the approach of the epoxidizing agent by the α-face of the molecule as a consequence of its concave shape due to the *cis*-ring fusion and is in agreement with our previous reports on the epoxidation of related compounds.[12,13] The spectral data for our synthetic **4** were coincident with those described for the natural[18] and synthetic[17] 11βH,13-dihydroestafiatin. To obtain (−)-compressanolide (**6**), we carried out the following two-step sequence, which has proved useful in the synthesis of 4α-OH guaianolides from the corresponding 3α,4α-epoxides.[12,13] Mild regioselective cleavage of the oxirane ring by treatment of **4** with PhSeNa/Ti(*i*-PrO)$_4$/DMF[24] gave hydroxyphenylselenide **8** in 92% yield, which by hydrogenolysis of the C−Se bond with carefully deactivated Raney Ni[25] afforded **6** in 65% yield. Starting material **8** was recovered (18%), but attempts to improve the conversion were unsuccessful, as the $\Delta^{10,14}$ double bond was too reactive and mixtures of **6** and its 10,14-dihydroderivatives were isolated in stronger conditions. The spectral data of our synthetic compound were fully consistent with those reported for the natural product isolated from *Michelia compressa*[20] and with those reported for the synthetic compound obtained by cyclization of dihydroparthenolide[20,22] or gallicin.[23]

For the synthesis of the $\Delta^{1,10}$ isomers **5** and **7** the starting material was hydroxyalkene **3**. 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 hydroxy alkene **3**. Thus, treatment of **3** with *m*-CPBA in the previously mentioned conditions gave a mixture of α- and β-epoxides in a ratio of 2.5:1 (84% yield). This ratio was improved to about 4:1 with the use of magnesium monoperoxyphthalate (MMPP),[26] a bulkier reagent, and in these conditions a mixture of α-epoxide **9** (74%) and β-epoxide **10** (19%) was obtained. The stereochemistry of the oxirane ring was assigned on the basis of the chemical shifts of H-6, with reference to those of compound **3**[11] in their ^{1}H NMR spectra.[17,27] Proton H-6 (which appears at δ 4.09 in compound **3**) shows a downfield shift to δ 4.31 in compound **10** due to the deshielding effect of the oxirane ring, whereas in compound **9** it appears at δ 3.96, a highfield shift that can be due to steric compression of the C_4-Me with a β-orientation in the α-epoxide. These assignments were confirmed by NOE experiments. Compound **9** shows a positive NOE among H_6 and H_3, $H_{2'}$ and H_{15}, whereas compound **10** shows a clear positive NOE only among H_6 and H_{14}. The formation of the C_1−C_{10} double bond was achieved regioselectively by treatment of compound **9** with triflic anhydride (Tf_2O)/pyridine in CH_2Cl_2.[11] The best results were obtained overnight at room temperature and afforded the expected tetrasubstituted alkene **5** in 66% yield (8.6 overall yield from santonin). The NMR spectra of **5** were consistent with its structure and were identical to the reported data for the natural[19] and synthetic[17b,27] 11βH,13-dihydroludartin. Regioselective opening of the C_3−C_4 oxirane ring with PhSeNa/Ti(*i*-PrO)$_4$/DMF followed by hydrogenolysis of the C−Se bond with deactivated Raney Ni gave compound **7** (67% yield for the two steps). The spectral and physical data for **7** were fully coincident with those reported for the synthetic (−)-11βH,-13-dihydromicheliolide,[20,22,23] but clearly differ from those for the natural product isolated from *Achillea millefolia*[21] in the chemical shifts for H-5, H-6, H-11, H-14, and H-15. In our synthetic compound H_5 appears at δ 2.62 and in the natural product at δ 2.36, whereas H_6, H_{11}, H_{14}, and H_{15} appear at higher field (δ 3.80, 2.24, 1.66, and 1.28, respectively) in comparison with those of the natural product (δ 4.27, 2.69, 1.72, and 1.44, respectively).

In summary, an efficient procedure for the preparation of compounds **4**−**7** from santonin (**1**) has been developed, which clearly improves on earlier reports of the syntheses of these compounds. Our method is based in the selective transformation of 10α-hydroxy-$\Delta^{3,4}$-guaianolides into 4α-hydroxy-$\Delta^{1,10}$-guaianolides or 4α-hydroxy-$\Delta^{10,14}$-guaianolides through mild regioselective opening of the corresponding 3α,4α-epoxides. As a consequence of these syntheses, the structures of natural products **4**−**6** have been confirmed, while the structure **7** appears to be inconsistent with the data previously reported for the natural product isolated from *A. millefolia*.[21]

Experimental Section

General Experimental Procedures. All reactions involving air or moisture sensitive materials were carried out under argon atmosphere. Commercial reagents and solvents were analytical grade or were purified by standard procedures prior to use. W-2 Raney Ni was prepared according to Mozingo's procedure[28] and deactivated by heating the ethanolic suspension at 60 °C for 3−4 days. Column chromatography was performed using silica gel (SDS, 40−60 μm). All melting points are uncorrected. Optical rotations were measured in $CHCl_3$ using a Perkin-Elmer 234 or a Polartronic D (Schmidt and Haensch) polarimeter. IR spectra were recorded as liquid films in NaCl for oils and as KBr disks for solids using a BIO-RAD Digilab Division FTS-7 unit. NMR spectra were run in $CDCl_3$, and chemical shifts were reported in ppm units and referenced to the solvent as internal standard. ^{1}H spectra including ^{1}H−^{1}H decoupling experiments were recorded with a Bruker AC 200 or a Varian Unity 400 spectrometer. ^{13}C NMR spectra including DEPT experiments were recorded with a Brucker AC 200 spectrometer at 50.3 MHz. Mass spectra were obtained with a Fisons Instruments VG Autospec, GC 8000 series spectrometer at 70 eV for electron impact or with methane as ionizing gas for CI. Compounds **2** and **3** were prepared according to our previously described procedure.[11]

(+)-3α,4α-Epoxy-1,5,7α*H*,6,11*βH*-guai-1(14)-en-6,12-olide (4) [(+)-11*βH*,13-Dihydroestafiatin]. To a precooled (−10 °C) solution of compound **2** (70 mg, 0.30 mmol) in $CHCl_3$ (3.6 mL) was added 86% *m*-CPBA (73 mg, 0.96 mmol), and the mixture was stirred at this temperature 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. The combined extract was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to leave an oil, which after chromatography (9:1 to 7:3 hexanes−EtOAc) afforded 5 mg (7%) of starting diene **2** and 45 mg (60%) of α-epoxide **4**: white crystals, mp 92−93 °C (hexanes−EtOAc); $[\alpha]^{22}_D$ +2.7° (*c* 1.46); IR (KBr) ν_{max} 1760, 1640, 1170 cm^{-1}; ^{1}H NMR (400 MHz), see ref 17; ^{13}C NMR (50.3 MHz) δ 178.3, 147.3 (C, C-12, C-10), 114.1 (CH_2, C-14), 80.7 (CH, C-6), 66.0 (C, C-4), 63.1, 50.4, 49.9, 44.2, 41.9 (CH, C-1, C-3, C-5, C-7, C-11), 33.6, 30.9, 30.9 (CH_2, C-2, C-8, C-9), 18.7, 13.2 (CH_3, C-13, C-15); EIMS *m*/*z* 248 (M^+, 30), 233 (77), 205 (20), 175 (40), 131 (51), 97 (100).

3*β*-Phenylselenyl-4α-hydroxy-1,5,7α*H*,6,11*βH*-guai-10(14)-en-6,12-olide (8). To a mixture of $NaBH_4$ (18 mg, 0.47 mmol) and PhSeSePh (133 mg, 0.40 mmol) under Ar was added DMF (1 mL), and the suspension was stirred at room temperature for 2 h. To the resulting solution were added via syringe AcOH (11 μL, 0.19 mmol), compound **4** (35 mg, 0.14 mmol) in DMF (1.7 mL), and Ti(*i*-PrO)$_4$ (54 μL, 0.18 mmol), and the mixture was stirred at room temperature for 23 h. After this time, the reaction was quenched with water and extracted with EtOAc. Usual workup and chromatography (5:5 hexanes−EtOAc) afforded 53 mg (92%) of hydroxy selenide **8**: yellow oil; IR (NaCl) ν_{max} 3530−3340, 1760, 1640, 1170, 890 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.70−7.60 (2H, m, 2Ar-H), 7.25−7.20 (3H, m, 3Ar-H), 4.97 (1H, s, H-14), 4.92 (1H, s, H-14′), 4.06 (1H, dd, *J* = 9.7, 10.6 Hz, H-6), 3.57 (1H, dd, *J* = 7.0, 13.4 Hz, H-3), 2.85 (1H, br dt, *J* = 10.3, 12.0 Hz, H-1), 2.63 (1H, dt, *J* = 3.5, 13.0 Hz, H-9), 2.29 (1H, dd, *J* = 10.6, 12.7 Hz, H-5), 2.18 (1H, dq, *J* = 7.0, 11.6 Hz, H-11), 2.20−1.95 (3H, m, 2H-2, H-8), 1.95−1.75 (2H, m, H-7, H-9′), 1.31 (3H, s, 3H-15), 1.40−1.10 (1H, m, H-8′), 1.21 (3H, d, *J* = 7.0 Hz, 3H-13); ^{13}C NMR (50.3 MHz) δ 177.8, 147.2 (C, C-12, C-10), 134.0, 128.9 (CH, Ar), 128.9 (C, Ar), 127.1 (CH, Ar), 112.5 (CH_2, C-14), 83.3 (CH, C-6), 80.4 (C, C-4), 54.7, 53.5, 51.4, 41.8, 41.3 (CH, C-1, C-3, C-5, C-7, C-11), 39.6, 34.9, 32.8 (CH_2, C-2, C-8, C-9), 21.1, 13.2 (CH_3, C-13, C-15).

(−)-4α-Hydroxy-1,5,7α*H*,6,11*βH*-guai-10(14)-en-6,12-olide (6) [(−)-Compressanolide]. Hydroxy selenide **8** (30 mg, 0.74 mmol) in EtOH (0.7 mL) was treated with deactivated ethanolic W-2 Raney Ni (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) and the solvent was evaporated at reduced pressure. Chromatography of the residue (7:3 hexanes−EtOAc) afforded 5 mg (18%) of starting material and 12 mg (65%) of compound **6** with the following features: colorless oil; $[\alpha]^{22}_D$ −3.6° (*c* 0.61); IR (NaCl) ν_{max} 3540−3360, 1770, 1640, 1170, 892 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.96 (1H, s, H-14), 4.93 (1H, s, H-14′), 4.03 (1H, dd, *J* = 9.6, 11.7 Hz, H-6), 2.96 (1H, dd, *J* = 8.8, 12.4 Hz, H-1), 2.63 (1H, dt, *J* = 4.0, 12.8 Hz, H-9), 2.24 (1H, dd, *J* = 10.0, 12.0 Hz, H-5), 2.22 (1H, dq, *J* = 6.8, 12.0 Hz, H-11), 2.25−2.18 (1H, m, H-3), 2.10 (1H, dq, *J* = 3.6, 13.0 Hz, H-8), 1.90−1.70 (5H, m, 2H-2, H-3′, H-7, H-9′), 1.28 (3H, s, 3H-15), 1.30−1.20 (1H, m, H-8′), 1.22 (3H, d, *J* = 6.8 Hz, 3H-13); ^{13}C NMR (50.3 MHz) δ 178.1, 148.5 (C, C-12, C-10), 112.0 (CH_2, C-14), 83.9 (CH, C-6), 79.8 (C, C-4), 55.6, 51.6, 44.1, 41.4 (CH, C-1, C-5, C-7, C-11), 40.2, 39.5, 32.9, 26.3 (CH_2, C-2, C-3, C-8, C-9), 24.1, 13.2 (CH_3, C-13, C-15); EIMS *m*/*z* 250 (M^+, 5), 232 (12), 159 (14), 119 (47), 43 (100).

(−)-3α,4α-Epoxy-10α-hydroxy-1,5,7α*H*,6,11*βH*-guaian-6,12-olide (9) and (+)-3*β*,4*β*-Epoxy-10α-hydroxy-1,5,7α*H*,6,-11*βH*-guaian-6,12-olide (10). To a solution of compound **3** (436 mg, 1.74 mmol) in MeOH (11.2 mL) was added MMPP (1.55 g, 3.49 mmol), and the mixture was stirred 5 h 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 (4:6 to 2:8 hexanes−EtOAc) afforded 343 mg (74%) of compound **9** and 88 mg (19%) of compound **10**. Data for **9**: white crystals, mp 118−120 °C (hexanes−EtOAc); $[\alpha]^{20}_D$ −13.3° (*c* 1.50); IR (KBr) ν_{max} 3540−3370, 1762, 1174, 989 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.96 (1H, t, *J* = 10.6 Hz, H-6), 3.26 (1H, br s, H-3), 2.55 (1H, dtd, *J* = 6.4, 10.6, 11.2 Hz, H-7), 2.31 (1H, dd, *J* = 7.6, 10.6 Hz, H-5), 2.25−2.03 (3H, m, H-1, H-8, H-11), 2.00 (1H, dd, *J* = 6.8, 13.6 Hz, H-2), 1.80−1.60 (3H, m, H-9, H-9′, −OH), 1.54 (3H, s, 3H-15), 1.49 (1H, t, *J* = 12.4 Hz, H-2′), 1.40−1.25 (1H, m, H-8′), 1.19 (3H, s, 3H-14), 1.17 (3H, d, *J* = 7.2 Hz, 3H-13); ^{13}C NMR (50.3 MHz) δ 178.6 (C, C-12), 80.8 (CH, C-6), 73.4, 65.8 (C, C-10, C-4), 61.6, 48.9, 48.3, 46.4, 43.1 (CH, C-1, C-3, C-5, C-7, C-11), 33.5 (CH_3, C-14), 31.2, 30.6, 25.3 (CH_2, C-2, C-8, C-9), 19.1, 13.1 (CH_3, C-13, C-15); CIMS *m*/*z* 267 (M^+ + 1, 22), 266 (M^+, 5), 251 (27), 249 (100), 231 (50), 203 (52); CIHRMS 267.1605 (M^+ + 1) (calcd for $C_{15}H_{23}O_4$, 267.1596). Data for **10**: white crystals, mp 116−119 °C (hexanes−EtOAc); $[\alpha]^{21}_D$ +15.3° (*c* 1.44); IR (KBr) ν_{max} 3560−3340, 1763, 1174, 980 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.31 (1H, t, *J* = 10.2 Hz, H-6), 3.20 (1H, d, *J* = 1.4 Hz, H-3), 2.46 (1H, td, *J* = 2.4, 10.4 Hz, H-1), 2.39 (1H, t, *J* = 10.4 Hz, H-5), 2.29 (1H, dd, *J* = 2.4, 16.0 Hz, H-2), 2.20 (1H, dq, *J* = 6.8, 12.0 Hz, H-11), 2.00 (1H, br dd, *J* = 10.4, 16.0 Hz, H-2′), 1.86 (2H, br d, *J* = 16.0 Hz, 2H-9), 1.66 (1H, br q, *J* = 10.4 Hz, H-7), 1.55−1.40 (1H, m, H-8), 1.49 (3H, s, 3H-15), 1.40−1.16 (1H, m, H-8′), 1.20 (3H, d, *J* = 6.8 Hz, 3H-13), 1.14 (3H, s, 3H-14); ^{13}C NMR (50.3 MHz) δ 178.3 (C, C-12), 82.6 (CH, C-6), 74.9, 67.2 (C, C-4, C-10), 65.1, 50.8, 50.4, 49.7 (CH, C-1, C-3, C-5, C-7), 45.1 (CH_2, C-2), 41.4 (CH, C-11), 29.5, 26.3 (CH_2, C-8, C-9), 24.3, 18.0, 12.7 (CH_3, C-13, C-14, C-15) CIMS *m*/*z* 267 (M^+ + 1, 15), 251 (31), 249 (100), 231 (92), 203 (60); CIHRMS 267.1593 (M^+ + 1) (calcd for $C_{15}H_{23}O_4$, 267.1596).

(+)-3α,4α-Epoxy-5,7α*H*,6,11*βH*-guai-(1,10)-en-6,12-olide (5) [(+)-11*βH*,13-Dihydroludartin]. To a solution of compound **9** (102 mg, 0.38 mmol) and pyridine (0.48 mL, 5.74 mmol) in CH_2Cl_2 (8.7 mL) at 0 °C and under argon was added dropwise via syringe triflic anhydride (0.4 mL, 2.37 mmol), and the mixture was stirred overnight at room temperature. The reaction was quenched with aqueous saturated $NaHCO_3$ and after usual workup (CH_2Cl_2) and chromatography (4:6 to 2:8 hexanes−EtOAc) afforded 10 mg (10%) of starting material and 62 mg (66%) of compound **5**: colorless oil; $[\alpha]^{22}_D$ +8.5° (*c* 0.46); IR (NaCl) ν_{max} 1774, 999 cm^{-1}; ^1H NMR (200 MHz) δ 3.63 (1H, dd, J = 8.8, 10.2 Hz, H-6), 3.36 (1H, br s, H-3), 2.97 (1H, br d, J = 10.0 Hz, H-5), 2.69 (1H, br d, J = 17.8 Hz, H-2), 2.41 (1H, d quint., J = 1.5, 17.8 Hz, H-2′), 2.19 (1H, dq, J = 7.0, 12.3 Hz, H-11), 2.20−2.00 (2H, m, 2H-9), 1.90−1.70 (2H, m, H-8, H-7), 1.66 (3H, d, J = 1.1 Hz, 3H-14), 1.60 (3H, s, 3H-15), 1.40−1.25 (1H, m, H-8′), 1.20 (3H, d, J = 7.0 Hz, 3H-13); ^{13}C NMR (50.3 MHz) δ 178.1, 135.3, 133.4 (C, C-12, C-1, C-10), 80.4 (CH, C-6), 67.2 (C, C-4), 63.8, 57.6, 51.9, 41.3 (CH, C-3, C-5, C-7, C-11), 34.4, 33.5, 27.4 (CH_2, C-2, C-8, C-9), 22.5, 19.1, 12.2 (CH_3, C-13, C-14, C-15); EIMS *m*/*z* 248 (M^+, 5), 233 (11), 205 (5), 152 (8), 95 (100).

3*β*-Phenylselenyl-4α-hydroxy-5,7α*H*,6,11*βH*-guai-1(10)-en-6,12-olide (11). The reagent was prepared as reported with $NaBH_4$ (12 mg, 0.31 mmol), PhSeSePh (87 mg, 0.26 mmol), and DMF (0.6 mL).To the resulting solution were added via syringe AcOH (8 μL, 0.14 mmol), α-epoxide **5** (20 mg, 0.08 mmol) in DMF (1 mL), and Ti(*i*-PrO)$_4$ (31 μL, 0.10 mmol), and the mixture was stirred at room temperature for 18 h. After this time, the reaction was quenched with water and extracted with EtOAc. Usual workup and chromatography (8:2 to 6:4 hexanes−EtOAc) afforded 2 mg (10%) of starting material **5** and 24 mg (74%) of compound **11**: yellow crystals, mp 152−154 °C (hexanes−EtOAc); IR (KBr) ν_{max} 3524−3400, 1774, 1180, 985 cm^{-1}; ^1H NMR (200 MHz) δ 7.70−7.60 (2H, m, 2Ar-H), 7.25−7.20 (3H, m, 3Ar-H), 3.81 (1H, t, J = 10.1 Hz, H-6), 3.52 (1H, dd, J = 8.1, 13.0 Hz, H-3), 2.81 (1H, br dd, J = 8.1, 16.5 Hz, H-2), 2.69 (1H, br d, J = 10.0 Hz, H-5), 2.50−2.10 (4H, m, H-2′, H-8, H-9, H-11), 1.95−1.65 (2H, m, H-7, H-9′), 1.64 (3H, d, J = 1.3 Hz, 3H-14), 1.35 (3H, s, 3H-15), 1.35−1.20 (1H, m, H-8′), 1.22 (3H, d, J = 7.0 Hz, 3H-13); ^{13}C NMR (50.3 MHz) δ 177.8 (C, C-12), 133.8 (CH, Ar), 132.0, 129.9 (C, C-1, C-10), 128.9 (CH, Ar), 128.8 (C, Ar), 127.1, 83.5 (CH, Ar, C-6), 81.1 (C, C-4), 57.9, 52.2, 53.5, 41.0 (CH, C-3, C-5, C-7, C-11), 39.1, 35.2, 26.8 (CH_2, C-2, C-8, C-9), 23.8, 20.0, 12.3 (CH_3, C-13, C-14, C-15).

(−)-4α-Hydroxy-5,7α*H*,6,11*βH*-guai-1(10)-en-6,12-olide (7) [(−)-11*βH*,13-Dihydromicheliolide]. Hydroxy selenide **11** (16 mg, 0.039 mmol) in EtOH (0.3 mL) was treated with deactivated ethanolic W-2 Raney Ni (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 **7** (9 mg, 90%): white crystals, mp 124−126 °C (hexanes−EtOAc) [lit.[22a] 124−127 °C ($CHCl_3$)]; $[\alpha]^{22}_D$ −4.7° (*c* 0.68) [lit.[23] $[\alpha]_D$ −8° (*c* 0.25)]; IR (KBr) ν_{max} 3600−3400, 1775, 1181, 987 cm^{-1}; ^1H NMR (400 MHz) δ 3.80 (1H, t, J = 10.5 Hz, H-6), 2.62 (1H, br d, J = 10.5 Hz, H-5), 2.59 (1H, br s, OH), 2.38 (1H, br dd, J = 8.0, 17.4 Hz, H-2), 2.24 (1H, dq, J = 6.8, 12.0 Hz, H-11), 2.20−2.10 (3H, m, H-3, 2H-9), 1.90−1.84 (1H, m, H-8), 1.84−1.70 (3H, m, H-2′, H-3′, H-7), 1.66 (3H, d, J = 1.6 Hz, 3H-14), 1.28 (3H, s, 3H-15), 1.26−1.20 (1H, m, H-8′), 1.22 (3H, d, J = 6.8 Hz, 3H-13); ^{13}C NMR (50.3 MHz) δ 178.2 (C, C-12), 131.9 (CH, C-1), 131.1 (C, C-10), 84.1 (CH, C-6), 80.2 (C, C-4), 58.2, 53.5, 41.1 (CH, C-5, C-7, C-11), 35.2, 30.0, 27.0 (CH_2, C-2, C-8, C-9), 23.7, 22.8, 12.3 (CH_3, C-13, C-14, C-15); CIMS *m*/*z* 250 (M^+,7), 234 (31), 233 (100), 232 (41), 159 (57); CIHRMS 250.2589 (M^+) (calcd for $C_{15}H_{22}O_3$ 250.1568).

Acknowledgment. Financial support from the 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 especially thankful to Conselleria de Cultura, Educació i Ciencia (Generalitat Valenciana) for a grant.

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NP020109F