Synthesis of (±)-11α-Hydroxy-3-oxo-6αH,7αH,10*β*Me-eudesman-1,2-4,5-dien-6,12-olide

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The synthesis of (±)-11α-hydroxy-3-oxo-6αH,7αH,10*β*Me-eudesman-1,2-4,5-dien-6,12-olide (**1**), previously isolated from *Melanoselinum decipiens*, is described, and its structure has been corrected.

The Umbelliferae (or Apiaceae) family of plants comprises around 3000 species distributed in 300 genera.[1] Many of them are commonly known for their strongly aromatic constituents. This family of plants produces a large number of coumarins, flavonoids, and phenylpropanoids.[2] These compounds are generally part of the essential oils of these plants, together with some monoterpenes, usually aldehydes such as cuminaldehyde or ketones such as carvone. Some members of this family are also an important source of sesquiterpenes and sesquiterpene lactones, especially those genera belonging to the *Laserpitieae* tribe.[3]

In 1986, Holub et al. proposed that the stereochemistry of all the sesquiterpene lactones isolated up to that date from Umbelliferae should be revised.[4] They reviewed more than 90 sesquiterpene lactones and proposed a different stereochemistry for them on the basis of spectral data. They discovered a common pattern for this kind of metabolite from this family. The most remarkable structural feature is the presence of a hydroxy or acyloxy moiety α to the carbonyl of the lactone, instead of the typical *exo*-methylene system. These metabolites also possess a *cis*-*β*,*β*-lactone fusion (epimeric at C-6 of most natural sesquiterpenolides). In the case of the eudesmanolides, the angular methyl is α-oriented. Figure 1 shows the most prominent differences between eudesmanolides from the Compositae (their main source) and those isolated from the Umbelliferae.

Holub et al. suggested the possibility that the conformation of the *trans*,*trans*-farnesyl diphosphate precursor in the Umbelliferae family may be different from that which gives rise to sesquiterpene lactones in the other families (Figure 2).[4]

From our efforts to isolate and synthesize metabolites from Umbelliferous plants, we have reported on the chemical components of *Melanoselinum decipiens*, a shrub endemic to the island of Madeira.[5,6] This study led to the isolation of 23 sesquiterpene lactones. We noticed that this plant not only produces sesquiterpene lactones that present the typical stereochemistry of the Umbelliferae, but also others that share some of the characteristics of those found in the Compositae. The structural pattern of this new kind of eudesmanolide from *M. decipiens* is depicted in Figure 3.

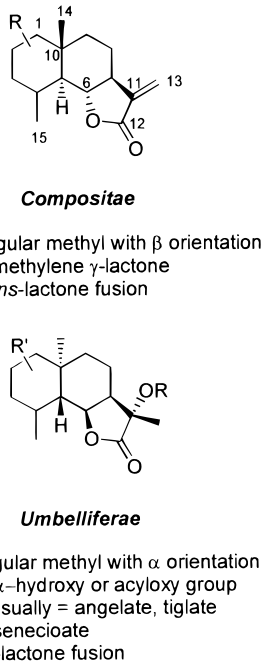

Figure 1.

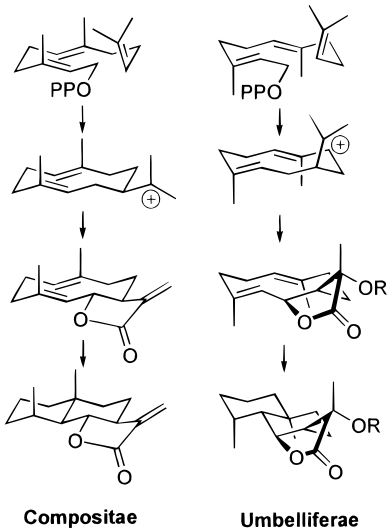

Figure 2. Proposed conformations for the *trans*,*trans*-farnesyl diphosphate.

Results and Discussion

When we reported the isolation of the title compound 11α-hydroxy-3-oxo-6αH,7αH,10*β*Me-eudesman-1,2-4,5-dien-6,12-olide (**1**), we assigned the stereochemistry of the angular methyl to be α, as present in most of the eudes-

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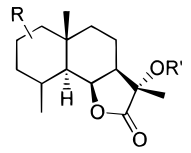
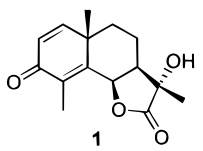


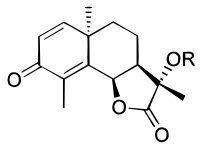
***M. decipiens* (Umbelliferae)**

- angular methyl with β orientation
- 11α–hydroxy or angeloyloxy group
- *cis*-lactone fusion

Figure 3.



1



2 R= angeloyl, Decipienin A
3 R= tigloyl
4 R= senecioyl

Figure 4. Different eudesmanolides isolated from *M. decipiens*.

manolides from the Umbelliferae. In the course of our synthesis of decipienin A (**2**) (Figure 4),[7] we realized that the structure we proposed for **1** did not match that of the synthetic product. We thus decided to carry out the synthesis of **1** in order to unambiguosly establish its stereochemistry. Herein, we report the synthesis of **1**, following the methodology developed by us for the synthesis of **2**, and correct the stereochemistry initially assigned.

Our synthesis began with racemic decalone (**5**), which was synthesized by our modification of the Kametani procedure (Scheme 1).[8] The lithium enolate of decalone (**5**) was treated with methyl pyruvate, affording ketoester **6** and its epimer at C-11.[7] It is worth noting that the alkyl group at C-7 is exclusively oriented in the axial position, presumably due to the presence of the axial angular methyl. The conversion of **6** to **7**, which displays the desired configuration at C-7, was carried out by treatment with *p*-TsOH in refluxing toluene to afford **7** in quantitative yield. The configuration of the different chiral centers was

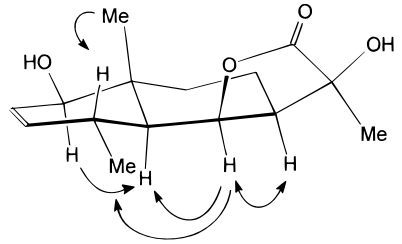
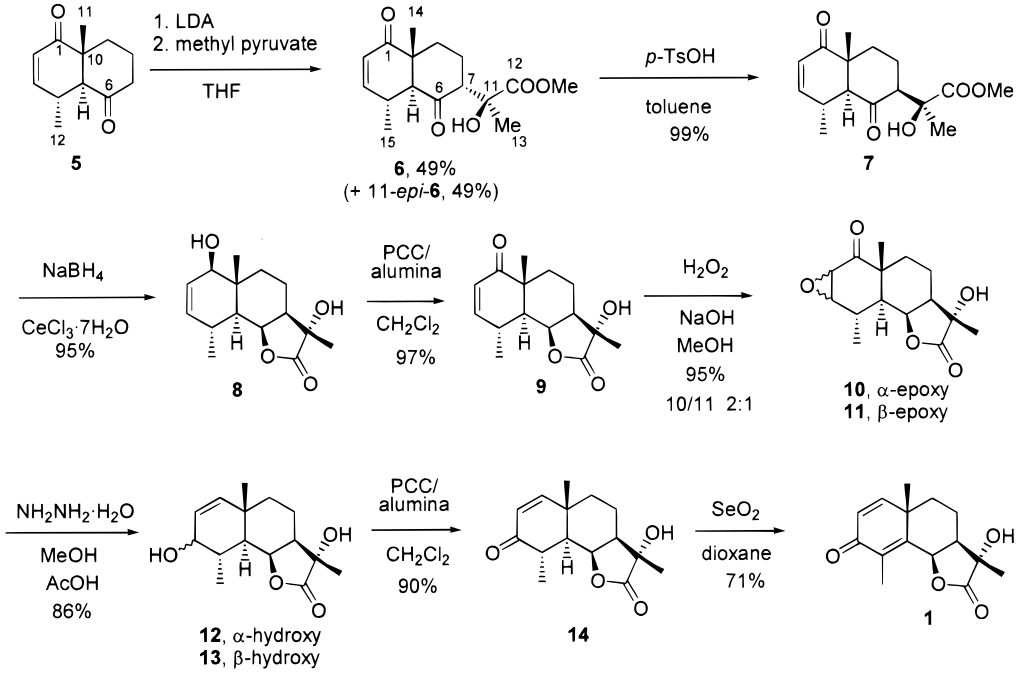


Figure 5. Observed NOEs for compound **8**.

confirmed in the subsequent steps of the synthesis by NOE measurements. Reduction of the carbonyl group on C-6 was performed with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$.[9] This reduction must be performed with great care. When excess reducing agent was used, and with long reaction times, a more polar product was formed, which was the result of the reduction of the ester group. If insufficient reducing agent is present in the reaction medium, the major product is that resulting from the reduction of the carbonyl at C-1. Furthermore, the cyclization to the lactone ring had to be induced by treatment in the workup with aqueous saturated sodium bicarbonate (see Experimental Section). The configuration of the resulting lactone **8** was determined by means of NOE experiments. The results are depicted in Figure 5.

Following our procedure for the synthesis of decipienin A, compound **8** was oxidized with pyridinium chlorochromate (PCC) on neutral alumina to yield enone **9**, which was then treated with basic H_2O_2 to provide a mixture of epoxides **10** and **11**. We were unable to purify **11**, as it decomposed in different chromatographic systems.[10] The mixture of epoxides underwent a Wharton rearrangement on treatment with hydrazine hydrate to afford the corresponding alcohols **12** and **13**. As in the previous case, the instability of **13** prevented its isolation. However, the oxidation of the mixture of both alcohols produced the enone **14**. Finally, treatment of **14** with SeO_2 afforded the desired lactone **1** in racemic form, the spectroscopic data of which were fully coincident with those of the natural product. Figure 6 displays the ^1H NMR of synthetic lactone

Scheme 1



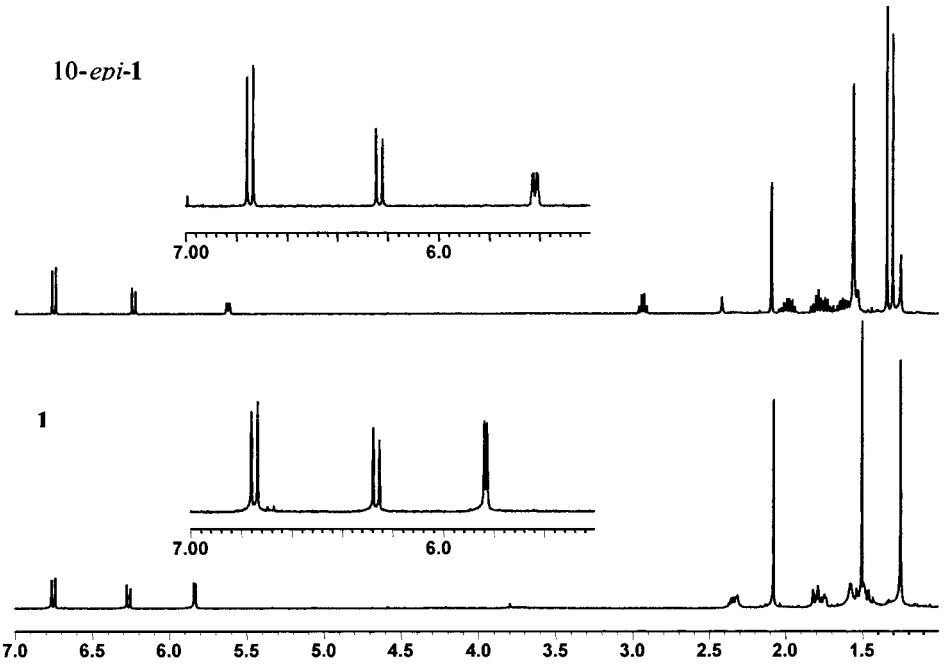


Figure 6. ^{1}H NMR spectra of compound **1** and its C(10)-epimer.

1 (which matches that of natural **1**), compared to synthetic 10-*epi*-**1** (the structure initally proposed).

The fact that this plant produces metabolites with two different configurations at C-10 implies that biogenetic hypotheses such as that proposed by Holub are too simple to explain the origin of these compounds. In this sense, more studies should be conducted to shed light on this problem.

Experimental Section

General Experimental Procedures. All nonaqueous reactions were carried out under nitrogen atmosphere. Air- and moisture-sensitive liquids and solutions were transferred via syringe. Reactions were monitored through TLC on commercial Si gel plates. Visualization of the developed plate was performed by fluorescence quenching and/or aqueous ceric ammonium molybdate/anisaldehyde stains. HPLC purification was carried out in a Merck-Hitachi L6270 equipped with a Si gel column (LiChrosorb Si 60, 7-μm particle size, 1 × 25 cm). THF, dioxane, diethyl ether, and toluene were distilled from sodium metal under nitrogen. Dichloromethane and triethylamine were distilled from calcium hydride prior to use. Melting points are uncorrected and were measured in a Reichert-Jung apparatus. NMR spectra were recorded on a Varian Gemini 200 or on a Varian Unity 400. Spectra were referenced internally to residual solvent signals. Data for ^{1}H are reported as follows: chemical shift (δ, ppm), integration, multiplicity, and coupling constant (J, Hz). Data for ^{13}C are reported in terms of chemical shift (δ, ppm). IR spectra were recorded in a Mattson Genesis Series FTIR, using NaCl plates, data are reported in cm^{-1}. Mass spectra were obtained in a Voyager GC−MS or in a VG Autospec-Q.

Condensation of Decalone (5) with Methyl Pyruvate. A 2 N LDA solution in hexanes (5.2 mL, 10.4 mmol) was added dropwise at −78 °C to a solution of decalone (**5**) (1.823 g, 9.50 mmol) in dry THF (150 mL). The mixture was stirred at that temperature for 30 min, and then methyl pyruvate (0.94 mL, 10.4 mmol) was added dropwise. The reaction was stirred at −78 °C for 2 h, then allowed to reach room temperature. The reaction mixture was poured onto saturated aqueous NH_4Cl (150 mL), then extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed by rotary evaporation to yield 2.792 g (98%) of a 1:1 mixture of **6** and its C-11-epimer. Purification was carried out by means of semipreparative HPLC (EtOAc/hexanes 1:2).

Hydroxy keto ester 6: colorless crystals; mp (EtOAc/hexanes) 114−115 °C. IR (thin film) ν 3475, 2958, 2883, 1732, 1693, 1660, 1451, 1430, 1392, 1376, 1256, 1208, 971 cm^{-1}; ^{1}H NMR δ 6.58 (1H, dd, J = 10.1, 2.2 Hz, H-3), 5.86 (1H, dd, J = 10.1, 2.2 Hz, H-2), 3.82 (3H, s, CO_2CH_3), 3.33 (1H, s, O*H*), 2.95 (1H, d, J = 9.6 Hz, H-5), 2.83 (1H, dqdd, J = 9.6, 6.8, 2.2, 2.2 Hz, H-4), 2.68 (1H, ddd, J = 14.8, 5.9, 5.7 Hz, H-9α), 2.57 (1H, dd, J = 8.8, 6.0 Hz, H-7), 2.10 (1H, dddd, J = 14.4, 10.0, 8.8, 5.7 Hz, H-8α), 1.93 (1H, dddd, J = 14.4, 6.0, 5.9, 5.5 Hz, H-8β), 1.43 (1H, ddd, J = 14.8, 10.0, 5.5 Hz, H-9β), 1.39 (3H, s, 3H-13), 1.07 (3H, d, J = 6.8 Hz, 3H-15), 0.97 (3H, s, 3H-14); ^{13}C NMR δ 211.4 (C-6), 201.9 (C-1), 176.9 (C-12), 153.2 (C-3), 125.6 (C-2), 75.7 (C-11), 58.8 (C-5), 54.9 (C-7), 53.1 (CO_2CH_3), 45.5 (C-10), 28.1 (C-9), 28.0 (C-4), 24.4 (C-13), 22.1 (C-14), 20.1 (C-8), 19.0 (C-15); MS m/z (rel int) 294 [M]$^+$ (9.7), 276 [M − H_2O]$^+$ (7.1), 235 [M − CO_2CH_3]$^+$ (46.1), 217 [M − CO_2CH_3 − H_2O]$^+$ (24.4), 192 [M − $C_4H_6O_3$]$^+$ (45.5), 175 [M − $C_4H_5O_3$ − H_2O]$^+$ (70.7), 82 (100), 77 (39.7), 55 (58.3); HRMS calcd for $C_{12}H_{16}O_2$ [M − $C_4H_6O_3$]$^+$ 192.1150, found 192.1166.

Isomerization of Compound 6. A solution of **6** (254 mg, 0.86 mmol) in dry toluene (50 mL) was treated with *p*-TsOH (33 mg, 0.17 mmol) and refluxed for 6 h. The mixture was allowed to cool, then washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum to yield pure **7** (249 mg, 99% yield).

Hydroxy keto ester 7: colorless crystals; mp (EtOAc/hexanes) 98−100 °C; IR (film) ν 3525, 2956, 2874, 1737, 1702, 1668, 1452, 1206, 1090, 978 cm^{-1}; ^{1}H NMR δ 6.60 (1H, dd, J = 10.1, 2.1 Hz, H-3), 5.84 (1H, dd, J = 10.1, 2.4 Hz, H-2), 3.78 (3H, s, CO_2CH_3), 3.61 (1H, s, O*H*), 2.89 (1H, dqdd, J = 10.0, 6.8, 2.7, 2.1 Hz, H-4), 2.71 (1H, dd, J = 12.6, 6.6 Hz, H-7), 2.61 (1H, d, J = 10.0 Hz, H-5), 2.21 (1H, dddd, J = 13.2, 13.2, 12.6, 4.0 Hz, H-8β), 2.20−2.15 (2H, m, H-8α, H-9β), 1.78 (1H, ddd, J = 14.2, 13.2, 4.7 Hz, H-9α), 1.40 (3H, s, 3H-13), 1.08 (3H, d, J = 6.8 Hz, 3H-15), 0.96 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.4 (C-6), 201.7 (C-1), 175.9 (CO_2CH_3), 153.2 (C-3), 125.4 (C-2), 73.8 (C-11), 62.1 (C-5), 59.4 (C-7), 52.4 (CO_2CH_3), 49.7 (C-10), 31.4 (C-9), 27.9 (C-4), 25.1 (C-8), 24.5 (C-13), 19.2 (C-15), 17.0 (C-14); EIMS m/z (rel int) 294 [M]$^+$ (0.5), 276 [M − H_2O]$^+$ (3.0), 235 [M − CO_2CH_3]$^+$ (100), 217 [M

$- CO_2CH_3 - H_2O]^+$ (6.8), 175 $[M - C_4H_5O_3 - H_2O]^+$ (52.4), 82 (30.4), 55 (20.7); HRMS *m/z* 294.1469 (calcd for $C_{16}H_{22}O_5$, 294.1467).

Reduction of 7 with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$. To a solution of ester **7** (202 mg, 0.69 mmol) in MeOH (15 mL) was added $CeCl_3 \cdot 7H_2O$ (512 mg, 1.37 mmol). The mixture was stirred for 20 min, after which time $NaBH_4$ (14 mg, 0.38 mmol) was added. After 30 min, aqueous saturated $NaHCO_3$ solution (20 mL) was added, and the mixture was stirred for an additional 20 min. The mixture was carefully neutralized with 1 N HCl. The MeOH was removed under vacuum, and the remaining aqueous layer was filtered and extracted with EtOAc (3 × 50 mL). The combined organics were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, EtOAc/hexanes, 1:1) to provide the lactone **8** (173 mg, 95%) as a crystalline solid.

1*β*,11α-Dihydroxy-4*β*H,5αH,6αH,7αH,10*β*Me-eudesman-2,3-en-6,12-olide (8): colorless crystals; mp (MeOH) 83−86 °C; IR (film) *ν* 3435, 3334, 2973, 2945, 2871, 1765, 1460, 1206, 928 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ* 5.59 (1H, ddd, *J* = 10.1, 2.2, 2.2 Hz, H-2), 5.42 (1H, ddd, *J* = 10.1, 2.5, 1.9 Hz, H-3), 5.03 (1H, dd, *J* = 3.8, 3.8 Hz, H-6), 3.87 (1H, m, H-1), 2.48 (1H, m, H-4), 2.18 (1H, ddd, *J* = 10.0, 6.4, 3.8 Hz, H-7), 1.99 (1H, m, H-9*β*), 1.61 (1H, m, H-8α), 1.41 (3H, s, 3H-13), 1.23 (1H, dd, *J* = 10.4, 3.8 Hz, H-5), 1.21 (1H, m, H-8*β*), 1.14 (1H, ddd, *J* = 8.9, 8.9, 2.0 Hz, H-9α), 1.09 (3H, d, *J* = 6.8 Hz, 3H-15), 0.91 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 177.2 (C-12), 135.0 (C-2), 128.5 (C-3), 77.6 (C-1), 77.5 (C-11), 76.2 (C-6), 47.1 (C-5), 45.8 (C-7), 36.1 (C-10), 34.7 (C-9), 29.4 (C-4), 19.0 (C-13), 18.2 (C-8), 18.1 (C-15), 12.7 (C-14); EIMS *m/z* (rel int) 266 $[M]^+$ (48.6), 251 $[M - CH_3]^+$ (10.6), 222 $[M - CO_2]^+$ (8.4), 207 $[M - CO_2 - CH_3]^+$ (7.5), 189 $[M - CO_2 - CH_3 - H_2O]^+$ (20.1), 193 $[M - C_3H_5O_2]^+$ (2.5), 177 $[M - C_3H_5O_3]^+$ (21.8), 161 $[C_{12}H_{17}]^+$ (54.6), 123 (75.0), 95 (100), 84 (99.0), 55 (47.6); HRMS *m/z* 266.1499 (calcd for $C_{15}H_{22}O_4$ 266.1518).

Oxidation of Lactone 8 with PCC on Neutral Alumina. A solution of lactone **8** (121 mg, 0.46 mmol) and PCC on neutral alumina (550 mg, 0.68 mmol, 1 mmol/806 mg) was stirred at room temperature for 2.5 h. The mixture was filtered through a plug of basic alumina, and the solvent was removed under vacuum to yield the lactone **9** (116 mg, 97%).

11α-Hydroxy-1-oxo-4*β*H,5αH,6αH,7αH,10*β*Me-eudesman-2,3-en-6,12-olide (9): colorless crystals; mp (EtOAc/hexanes) 227−229 °C; IR (film) *ν* 3391, 2977, 2948, 1755, 1674, 1456, 1379, 1197, 965 cm^{-1}; ^1H NMR *δ* 6.74 (1H, dd, *J* = 10.0, 2.0 Hz, H-3), 5.88 (1H, dd, *J* = 10.0, 2.8 Hz, H-2), 5.05 (1H, dd, *J* = 3.6, 3.6 Hz, H-6), 2.88 (1H, dqdd, *J* = 10.4, 7.4, 2.8, 2.0 Hz, H-4), 2.52 (1H, s, O*H*), 2.19 (1H, ddd, *J* = 10.4, 6.4, 3.6 Hz, H-7), 2.04 (1H, ddd, *J* = 14.0, 13.6, 2.8 Hz, H-9*β*), 1.70 (1H, m, H-8α), 1.65 (1H, dd, *J* = 10.4, 3.6 Hz, H-5), 1.44 (3H, s, 3H-13), 1.34 (1H, ddd, *J* = 13.6, 3.5, 3.5 Hz, H-9α), 1.27 (3H, d, *J* = 7.4 Hz, 3H-15), 1.23 (1H, dddd, *J* = 13.6, 10.4, 3.5, 2.8 Hz, H-8*β*), 1.12 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 203.7 (C-1), 177.0 (C-12), 154.5 (C-3), 126.1 (C-2), 77.5 (C-11), 76.4 (C-6), 48.3 (C-5), 45.3 (C-7), 43.0 (C-10), 30.7 (C-4), 29.9 (C-9), 18.8 (C-13), 18.1 (C-8), 17.6 (C-14), 17.4 (C-15); MS *m/z* (rel int) 265 $[M + 1]^+$ (36.9), 247 $[M + 1 - H_2O]^+$ (1.9), 220 $[M - CO_2]^+$ (67.5), 205 $[M - CO_2 - CH_3]^+$ (14.6), 202 $[M - CO_2 - H_2O]^+$ (15.9), 187 $[M - CO_2 - H_2O - CH_3]^+$ (29.4), 175 $[M - C_3H_5O_3]^+$ (17.2), 159 $[C_{11}H_{11}O]^+$ (32.3), 136 (49.2), 123 (74.4), 82 (100), 55 (22.0); HRMS *m/z* 264.1343 (calcd for $C_{15}H_{20}O_4$, 264.1362).

Epoxidation of Lactone 9. A 35% solution of hydrogen peroxide (122 *μ*L, 1.18 mmol) and 6 N aqueous NaOH (80 *μ*L, 0.48 mmol) was added to a solution of lactone **9** (125 mg, 0.47 mmol) in MeOH (5 mL). After stirring for 2.5 h, the reaction was cooled to 0 °C and neutralized with 1 N HCl. The mixture was extracted with EtOAc (3 × 10 mL), and the organic phase was dried over anhydrous Na_2SO_4. Removal of the solvent afforded a mixture of the epoxides **10** and **11** (127 mg, 95%). In previous runs of this reaction, analysis by ^1H NMR showed a 2:1 ratio of **10** to **11**. Nevertheless, lactone **11** is a very unstable compound. Its purification on Si gel usually led to complex mixtures. Only a small amount of **11** could be obtained for analytical purposes. Purification on basic alumina was unsuccessful. Therefore, the crude mixture of **10** and **11** was used in the next step without further purification.

2α,3α-Epoxy-11α-hydroxy-4*β*H,5αH,6αH,7αH,10*β*Me-eudesman-6,12-olide (10): colorless crystals; mp (EtOAc/hexanes) 239−242 °C; IR (film) *ν* 3401, 2980, 2954, 2875, 1767, 1697, 1455, 1443, 1380, 1352, 1263, 1231, 1212, 1133, 1052, 983 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ* 4.97 (1H, dd, *J* = 4.0, 4.0 Hz, H-6), 3.45 (1H, dd, *J* = 3.6, 1.2 Hz, H-3), 3.26 (1H, d, *J* = 3.6 Hz, H-2), 2.52 (1H, dqd, *J* = 11.2, 6.8, 1.2 Hz, H-4), 2.15 (1H, ddd, *J* = 12.8, 6.4, 4.4 Hz, H-9α), 2.05 (1H, ddd, *J* = 13.6, 4.0, 3.6 Hz, H-7), 1.66 (1H, dd, *J* = 11.2, 4.0 Hz, H-5), 1.65 (1H, m, H-8*β*), 1.42 (3H, s, 3H-13), 1.34 (3H, d, *J* = 6.8 Hz, 3H-15), 1.29 (1H, m, H-8α), 1.12 (1H, m, H-9*β*), 1.05 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 205.3 (C-1), 176.7 (C-12), 77.3 (C-11), 76.7 (C-6), 58.1 (C-3), 52.8 (C-2), 45.2 (C-7), 43.9 (C-10), 37.8 (C-5), 29.6 (C-9), 27.9 (C-4), 19.0 (C-8), 17.9 (C-13), 17.8 (C-14), 15.4 (C-15); EIMS *m/z* (rel int) 280 $[M]^+$ (4.1), 251 $[C_{14}H_{19}O_4]^+$ (20.0), 236 $[M - CO_2]^+$ (86.1), 218 $[M - CO_2 - H_2O]^+$ (8.6), 203 $[M - CO_2 - H_2O - CH_3]^+$ (11.3), 193 $[M - C_3H_3O_3]^+$ (12.4), 175 $[M - C_3H_3O_3 - H_2O]^+$ (40.9), 157 $[M - C_3H_3O_3 - 2 \times H_2O]^+$ (14.2), 147 $[C_{10}H_{11}O]^+$ (55.6), 123 (100), 95 (45.3), 84 (60.4), 71 (82.3); HRMS *m/z* 280.1260 (calcd for $C_{15}H_{20}O_5$ 280.1311).

2*β*,3*β*-Epoxy-11α-hydroxy-4*β*H,5αH,6αH,7αH,10*β*Me-eudesman-6,12-olide (11): amorphous solid; IR (film) *ν* 3453, 2983, 2938, 2879, 1774, 1708, 1453, 1216, 963 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ* 4.93 (1H, dd, *J* = 3.8, 3.8 Hz, H-6), 3.34 (1H, d, *J* = 3.6 Hz, H-2), 3.20 (1H, d, *J* = 3.6 Hz, H-3), 2.70 (1H, dq, *J* = 12.0, 7.2 Hz, H-4), 2.11 (1H, ddd, *J* = 12.8, 6.8, 4.4 Hz, H-9α), 1.90 (1H, ddd, *J* = 14.0, 3.8, 3.4 Hz, H-7), 1.63 (1H, dddd, *J* = 13.2, 6.8, 3.4, 3.4 Hz, H-8α), 1.46 (1H, dd, *J* = 12.0, 3.8 Hz, H-5), 1.41 (3H, s, 3H-13), 1.31 (1H, m, H-9*β*), 1.30 (3H, d, *J* = 7.2 Hz, 3H-15), 1.24 (3H, s, 3H-14), 1.18 (1H, m, H-8*β*); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 209.0 (C-1), 176.6 (C-12), 77.4 (C-11), 76.9 (C-6), 63.9 (C-2), 53.8 (C-3), 50.2 (C-5), 45.2 (C-7), 44.1 (C-10), 31.3 (C-9), 27.9 (C-4), 18.9 (C-15), 17.5 (C-8), 17.1 (C-13), 16.9 (C-14); EIMS *m/z* (rel int) 280 $[M]^+$ (2.9), 251 $[C_{14}H_{19}O_4]^+$ (46.5), 236 $[M - CO_2]^+$ (89.2), 218 $[M - CO_2 - H_2O]^+$ (12.3), 203 $[M - CO_2 - H_2O - CH_3]^+$ (10.8), 193 $[M - C_3H_3O_3]^+$ (12.0), 175 $[M - C_3H_3O_3 - H_2O]^+$ (41.9), 157 $[M - C_3H_3O_3 - 2 \times H_2O]^+$ (12.1), 147 $[C_{10}H_{11}O]^+$ (58.0), 123 (100), 105 (63.0), 93 (66.5), 84 (66.3), 71 (90.1); HRMS *m/z* 280.1302 (calcd for $C_{15}H_{20}O_5$, 280.1311).

Wharton Rearrangement of Epoxy Lactone 10. Hydrazine hydrate (130 *μ*L) and concentrated HOAc (0.4 mL) was added to a solution of lactone **10** (53 mg, 0.19 mmol) in MeOH (10 mL). After stirring for 8 h, the reaction mixture was diluted with H_2O (10 mL), neutralized carefully with aqueous saturated $NaHCO_3$ solution, and extracted with EtOAc (3 × 20 mL). The solvent was removed under vacuum, and the resulting residue was chromatographed by HPLC (EtOAc/hexanes 2:3) to yield lactone **12** (43 mg, 86%). This reaction could also be conducted using the mixture of **10** and **11**, in which case, a mixture of the hydroxy lactones **12** and **13** were obtained. As in the case of epoxy lactone **11**, we were unable to purify lactone **13**, due to its rapid decomposition on different chromatographic systems.

3α,11α-Dihydroxy-4*β*H,5αH,6αH,7αH,10*β*Me-eudesman-1,2-en-6,12-olide (12): amorphous solid; IR (film) *ν* 3452, 3367, 2931, 2880, 2857, 1760, 1458, 1381, 1196, 1064, 972 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ* 5.66 (1H, dd, *J* = 9.8, 4.4 Hz, H-2), 5.61 (1H, d, *J* = 9.8 Hz, H-1), 5.00 (1H, dd, *J* = 3.6, 3.6 Hz, H-6), 4.05 (1H, dd, *J* = 4.4, 4.0 Hz, H-3), 2.25−2.10 (2H, m, H-4, H-7), 1.65−1.50 (2H, m, H-8α, H-9*β*), 1.56 (1H, dd, *J* = 11.2, 3.6 Hz, H-5), 1.42 (3H, s, 3H-13), 1.36 (1H, ddd, *J* = 13.8, 13.8, 3.0 Hz, H-9α), 1.28 (1H, m, H-8*β*), 1.16 (3H, d, *J* = 7.2 Hz, 3H-15), 0.96 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 177.4 (C-12), 142.6 (C-1), 125.5 (C-2), 77.4 (C-11), 77.1 (C-6), 69.0 (C-3), 45.8 (C-7), 42.1 (C-5), 36.4 (C-9), 34.8 (C-10), 32.1 (C-4), 20.2 (C-14), 19.0 (C-13), 18.8 (C-8), 13.1 (C-15); EIMS *m/z* (rel int) 266 $[M]^+$ (16.5), 251$[M - CH_3]^+$ (3.5), 177 $[M - C_3H_5O_3]^+$ (20.7), 167 (31.2), 159 $[M - C_3H_5O_3 - H_2O]^+$

(13.6), 149 $[C_{11}H_{17}]^+$ (100), 71 (34.7), 57 (56.3); HRMS *m/z* 266.1495 (calcd for $C_{15}H_{22}O_4$, 266.1518).

Oxidation of Lactone 12 with PCC on Neutral Alumina. A solution of lactone **12** (37 mg, 0.14 mmol) in CH_2Cl_2 was treated with PCC on neutral alumina (224 mg, 0.28 mmol, 1 mmol/806 mg) for 2.5 h. The mixture was then filtered through basic alumina and, after removal of the solvent, was chromatographed (SiO_2, EtOAc/hexanes, 2:3) to yield pure lactone **14** (33 mg, 90%). The crude mixture of **12** and **13** can also be oxidized with PCC to give **14** as a single product following the same procedure.

11α-Hydroxy-3-oxo-4*β*H,5αH,6αH,7αH,10*β*Me-eudesman-1,2-en-6,12-olide (14): colorless crystals; mp (EtOAc/hexanes) 169−171 °C; IR (film) *ν* 3435, 2974, 2944, 1765, 1672, 1376, 1197, 1121, 964 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ* 6.65 (1H, d, *J* = 10.0 Hz, H-1), 5.85 (1H, d, *J* = 10.0 Hz, H-2), 4.99 (1H, dd, *J* = 3.6, 3.6 Hz, H-6), 2.75 (1H, dq, *J* = 13.6, 6.8 Hz, H-4), 2.41 (1H, br s, O*H*), 2.24 (1H, ddd, *J* = 12.8, 6.4, 4.2 Hz, H-9α), 1.77 (1H, dd, *J* = 13.6, 3.6 Hz, H-5), 1.70 (1H, m, H-7), 1.69 (1H, m, H-8*β*), 1.46 (1H, ddd, *J* = 12.8, 12.8, 3.6 Hz, H-9*β*), 1.44 (3H, s, 3H-13), 1.36 (1H, m, H-8α), 1.27 (3H, d, *J* = 6.8 Hz, 3H-15), 1.15 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 201.4 (C-3), 177.0 (C-12), 159.0 (C-1), 126.3 (C-2), 77.4 (C-11), 76.3 (C-6), 48.1 (C-9), 45.0 (C-7), 40.0 (C-4), 35.4 (C-5), 35.0 (C-10), 19.2 (C-13), 18.9 (C-14), 18.5 (C-8), 11.3 (C-15); EIMS *m/z* (rel int) 264 $[M]^+$ (2.7), 235 $[C_{14}H_{19}O_3]^+$ (100), 220 $[M - CO_2]^+$ (94.0), 205 $[M - CO_2 - CH_3]^+$ (11.4), 193 (55.2), 175 $[M - C_3H_5O_3]^+$ (73.8), 161 $[M - C_3H_4O_3 - CH_3]^+$ (64.9), 147 $[M - C_3H_3O_3 - 2\ H\ CH_3]^+$ (32.7), 95 $[C_6H_7O]$ (82.5); HRMS *m/z* 264.1354 (calcd for $C_{15}H_{20}O_4$, 264.1362).

Oxidation of Lactone 14 with SeO_2. A solution of lactone **14** (27 mg, 0.10 mmol) and SeO_2 (35 mg, 0.31 mmol) was refluxed in dioxane (5 mL) for 14 h. The reaction mixture was allowed to cool to room temperature, then filtered through Celite. After removal of solvent, the residue was purified by HPLC (SiO_2, EtOAc/hexanes, 2:3) to afford lactone **1** (19 mg, 71%). Starting lactone **14** (6 mg) was also recovered.

11α-Hydroxy-3-oxo-6αH,7αH,10*β*Me-eudesman-1,2-4,5-en-6,12-olide (1): colorless crystals; mp (CH_2Cl_2) 207−209 °C; IR (film) *ν* 3432, 2948, 2923, 1763, 1668, 1633, 1448, 1197, 966 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ* 6.75 (1H, d, *J* = 9.8 Hz, H-1), 6.26 (1H, d, *J* = 9.8 Hz, H-2), 5.83 (1H, d, *J* = 4.4 Hz, H-6), 2.35 (1H, m, H-7), 2.31 (1H, br s, O*H*), 2.08 (3H, s, 3H-15), 1.80 (1H, m, H-9*β*), 1.76 (1H, m, H-8α), 1.57 (1H, m, H-9α), 1.50 (3H, s, 3H-13), 1.50 (1H, m, H-8*β*), 1.25 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 180.0 (C-3), 176.6 (C-6), 157.0 (C-1), 148.0 (C-5), 138.1 (C-4), 126.0 (C-2), 77.1 (C-11), 76.0 (C-6), 47.0 (C-7), 38.9 (C-10), 34.3 (C-9), 24.8 (C-14), 19.4 (C-8), 18.2 (C-13), 11.1 (C-15); EIMS *m/z* (rel int) 262 $[M]^+$ (2.7), 234 $[M - CO]^+$ (4.0), 218 $[M - CO_2]^+$ (25.3), 203 $[M - CO_2 - CH_3]^+$ (30.3), 175 $[M - C_3H_3O_3]^+$ (100), 159 $[C_{12}H_{15}]^+$ (33.8), 148 (37.9), 135 (41.4), 91 $[C_7H_7]^+$ (29.0); HREIMS *m/z* 262.1188 (calcd for $C_{15}H_{18}O_4$, 262.1205).

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References and Notes

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(10) A sample of **11** was obtained for analytical purposes. NOE measurements of **10** and **11** confirmed their stereochemistry.

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