Transformation of α-Santonin into 7-Hydroxyeudesmanes[1)]

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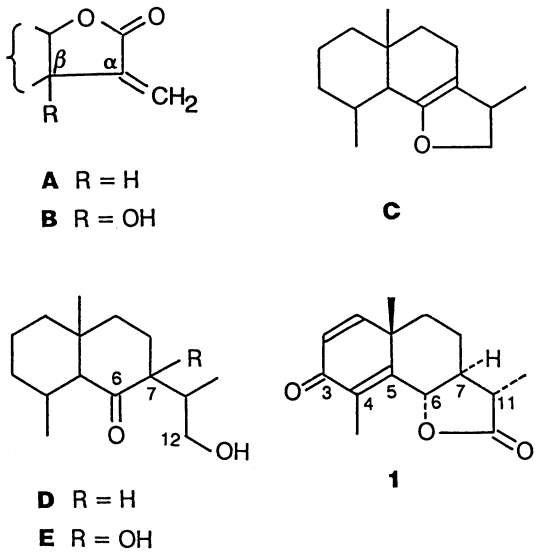
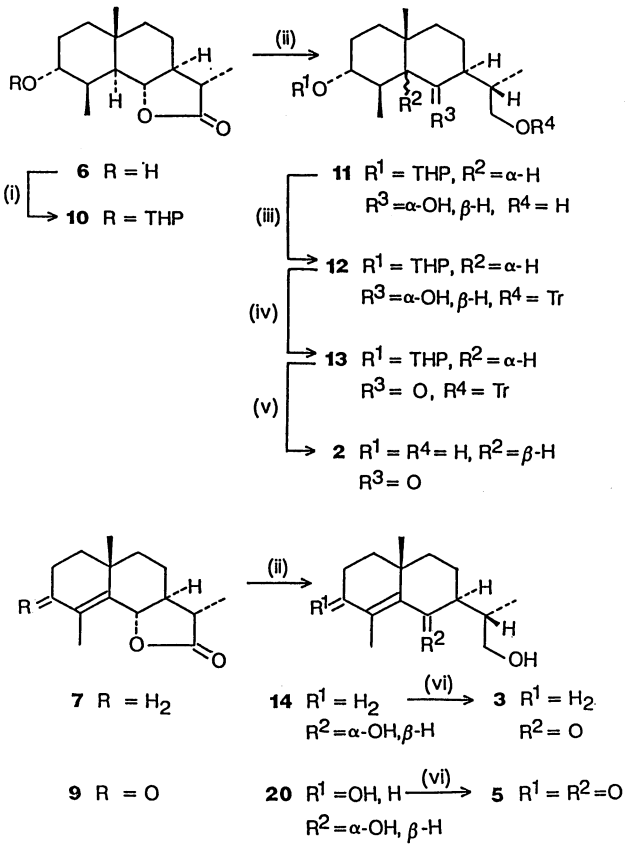
Autoxidation of (11*S*)-12-hydroxy-7α-eudesmane-3,6-dione in the presence of *p*-toluenesulfonic acid gave 6,12-epoxy-11β-eudesma-4,6-dien-3-one, which was oxidized with *m*-chloroperoxybenzoic acid to give (11*R*)-7α,12-dihydroxyeudesm-4-ene-3,6-dione. Transformation of some other 12-hydroxyeudesman-6-ones into 7,12-dihydroxyeudesman-6-ones was also examined.

Cytotoxic, antitumor, and other biological activities of many sesquiterpenes have been attributed to the presence of the α-methylene-γ-lactone unit **A**. The presence of a hydroxyl group adjacent to the α-methylene group may enhance the biological activity and is a comnon feature among many sesquiterpene lactones showing in vivo antitumor activity.[2)] The β-hydroxy-α-methylene-γ-lactone unit **B** is found in eudesmane,[3)] guaiane,[3d)] elemane,[4)] and germacrane-type[3d,4,5)] sesquiterpenes. 7α-Hydroxyfrullanolide, the main antimicrobial component of a medically important Indian plant *Sphaeranthus indicus* Linn.,[3a,b,c)] 7α-hydroxysantamarine,[3d)] and 7α-hydroxyreynosin[3d)] are typical examples of eudesmane-type sesquiterpenes possessing the β-hydroxy-α-methylene-γ-butyrolactone unit **B**.[6)] Furthermore, biologically interesting 7α-hydroxyeudesmanes,[7)] such as 7α-hydroxycostal and 7α-hydroxycostol, sweet potato phytoalexins,[7d)] have also been isolated. In the course of our natural product synthesis from α-santonin (**1**)[8)] we now report the transformation of α-santonin (**1**) into 7,12-dihydroxyeudesman-6-ones, which may be intermediates in the synthesis of natural 7-hydroxyeudesmanes including 7-hydroxyeudesman-12,6-olides.

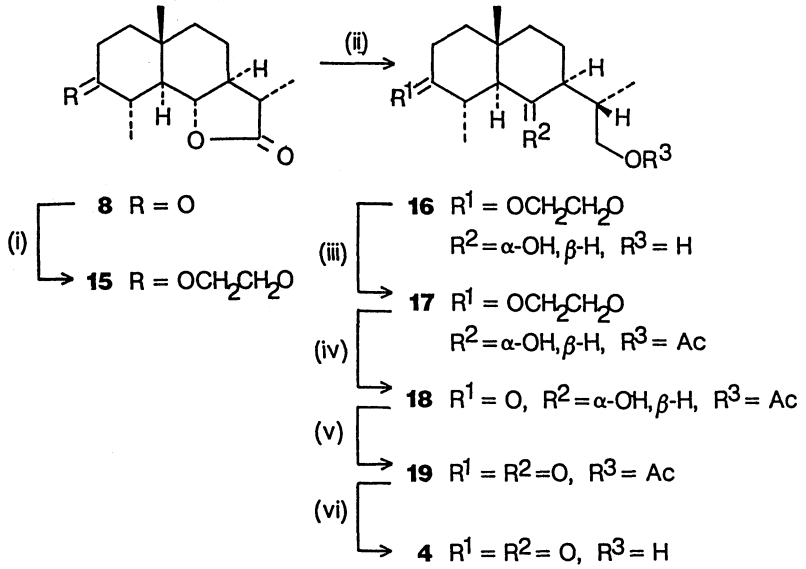
Introduction of a hydroxyl group at C-7 on the eudesmane skeleton was examined by oxidation of the enol ethers **C** derived from 12-hydroxyeudesman-6-ones **D** (**D**→**C**→**E**). Substrates of oxidation, 12-hydroxyeudesman-6-ones **2**—**5**, were synthesized from compounds **6**—**9**, respectively (Schemes 1 and 2). The starting materials **6**—**9** were prepared from α-santonin (**1**) following the reported procedures.[9)]

Treatment of 3α,12-dihydroxyeudesman-6-one (**2**) with *p*-toluenesulfonic acid (TsOH) in tetrahydrofuran (THF) followed by oxidation with *m*-chloroperoxybenzoic acid (MCPBA) gave a complex mixture and only 3α,5,12-trihydroxyeudesman-6-one (**21**), [δ=2.45 (dq, *J*=5.5 and 7.5 Hz, 4-H)] was isolated in poor yield (<5%). 12-Hydroxyeudesm-4-en-6-one (**3**) was treated with TsOH in benzene to give an insepara-

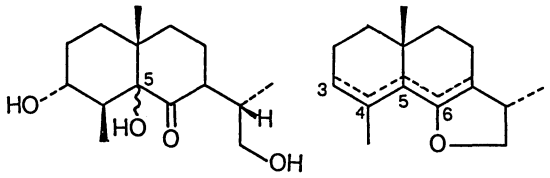




Scheme 1. Reagents: (i) DHP, TsOH, (ii) $LiAlH_4$, (iii) TrCl, DMAP, Et_3N, (iv) $CrO_3 \cdot 2$pyridine, (v) H_3O^+, (vi) MnO_2.



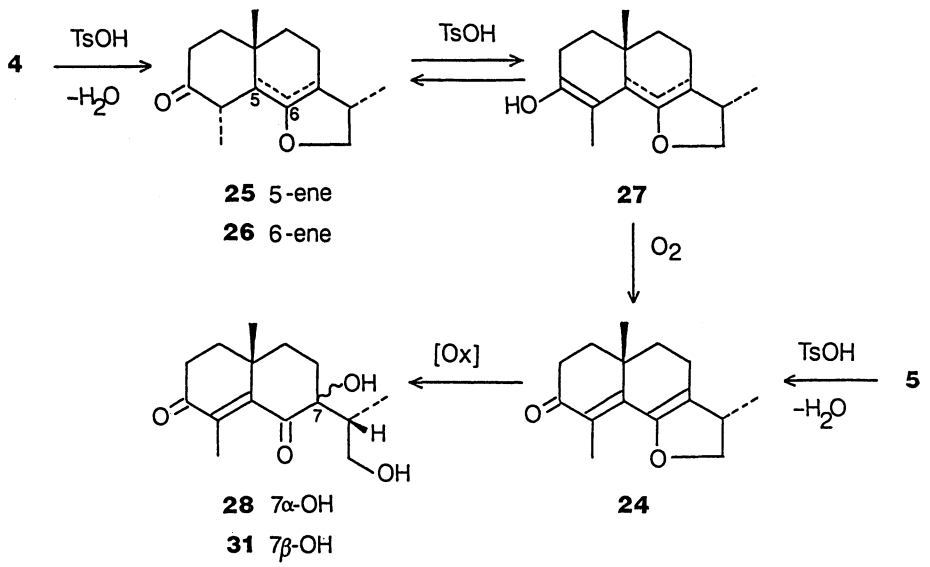
Scheme 2. Reagents: (i) ethylene glycol, TsOH, (ii) $LiAlH_4$, (iii) Ac_2O, pyridine, (iv) H_3O^+, (v) Jones reagent, (vi) OH^-.



21 **22** 3,5-diene
23 4,6-diene

ble mixture of enol ethers **22** [^{1}H NNR δ=5.20 (br s, 3-H)] and **23** in a ratio of 2:3. Oxidation of the enol ethers **22** and **23** with MCPBA yielded a complex mixture and the desired 7-hydroxy derivative was not isolated. This may be due to the oxidation of the 3-ene and 4-ene double bonds in addition to that of the enol ether moiety.

Treatment of a benzene solution of 12-hydroxyeudesmane-3,6-dione (**4**) with TsOH at room temperature in air gave the dienone **24** in 57% yield (Scheme 3). The UV [(CH_3OH) 336 (ε 12000), 252 (5300), and 210 nm (3500)], IR (1665, 1633, and 1583 cm^{-1}), and ^{13}C NNR [δ=199.76 (C-3), 149.52 (C-5), 146.93 (C-6), 128.36 (C-4), and 125.41 (C-7)] spectra indicated the presence of a conjugated dienone moiety in **24**. The two-dimensional ^{1}H-^{1}H shift-correlation spectrum (COSY) of **24** further showed the presence of partial structures, -O-CH_2CH(CH_3)- and -CH_2CH_2C(CH_3)-CH_2CH_2-. On the other hand, when **4** was treated with TsOH in benzene under nitrogen, an inseparable mixture of enol ethers **25** and **26** was yielded in a ratio of 1:2. The mixture was further transformed into **24**



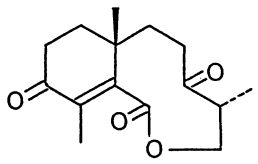
Scheme 3.

in the presence of TsOH in air. The dehydrogenation reaction, however, did not proceed without TsOH; this indicates that the reaction proceeded via the acid-catalyzed enolization of C-3 carbonyl group of the enol ethers **25** and/or **26**. The intermediately formed electron rich diene(s) **27** may be oxygenated with molecular oxygen.[10]

As an acyclic model of **4**, 8-hydroxy-2,5-octanedione was prepared from γ-butyrolactone (cf. Experimental).[11] Autoxidation of the diketone under similar conditions did not proceed. Base-catalyzed autoxidation of acyclic 1,4-diketones to 2-ene-1,4-diones has not been reported. Under acidic conditions only cyclic 1,4-diketones may be autoxidized to 2-ene-1,4-diones. To our knowledge the conversion reported herein may be the first example of the acid-catalyzed autoxidation of 1,4-diketones to 2-ene-1,4-diones.[12]

6,12-Epoxyeudesma-4,6-dien-3-one (**24**), which was also derived from 12-hydroxyeudesm-4-ene-3,6-dione (**5**), was oxidized with MCPBA to give 7α,12-dihydroxyeudesm-4-ene-3,6-dione (**28**) in 54% yield along with the lactone **29** (10% yield).[13]

The electron-deficient 4-ene double bond in **24** was



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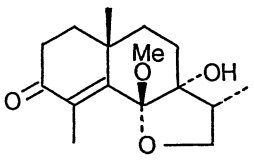

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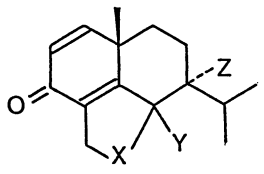
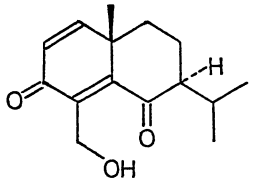
thus not affected by the oxidizing agent. The stereochemistry of the newly introduced C-7 hydroxyl group was determined to be α by the following outcome. Oxidation of the dienone **24** with MCPBA in



32 X = O, Y = Z = OH

33 X = O-O, Y = OH, Z = H

35 X = O or O-O, Y,Z = 6-ene



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methanol gave **30** in 51% yield.[14] The down-field shift of 8α-signal [δ=1.10 to 3.04 (ddd, *J*=14.0, 4.3, and 2.5 Hz); assigned by the COSY spectra measured in C_6D_6] by addition of trichloroacetyl isocyanate and the nuclear Overhauser enhancement of OMe signal on irradiation of 10β-Me revealed the stereochemistry of the hydroxyl and methoxy groups. Furthermore, the dienone **24** was oxygenated upon standing in air to give 7-hydroxy derivatives **28** and **31** in low and variable yields.[15]

Benghalensin **B** (**32**), a 7-hydroxyeudesmane isolated from *Meriandra benghalensis* (Labiatae),[7c] is assumed to be yielded from benghalensin **A** (**33**) or 15-hydroxyeudesma-1,4-diene-3,6-dione (**34**) by oxygenation of the enol ether **35**. The hydroxy diketone **34** may be yielded from **33**.

Compounds **28** and **30** may be intermediates in the synthesis of natural 7-hydroxyeudesmanes.

Experimental

Melting points were determined on a hot block melting point apparatus and are uncorrected. IR spectra were taken on a JASCO A-3 spectrometer. UV spectra were taken on a Shimadzu UV 240 spectrometer. ^{1}H NMR spectra were recorded on a JEOL GX-270 (270 MHz) spectrometer with chloroform-*d* as solvent (unless otherwise stated) and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on the instrument (67.8 MHz) with chloroform-*d* as solvent and internal standard (δ=77.0). Mass spectra were obtained on a JEOL DX-300 mass spectrometer using electron impact mode (70 eV). Accurate mass measurements were recorded on the mass spectrometer. Optical rotations were determined on a JASCO DIP-181 polarimeter. Precoated Merck Kieselgel 60 F_{254} was used for general analytical purposes. Silica gel (Wakogel C-300) was used for flash chromatography.

3α-(Tetrahydro-2-pyranyloxy)-4α,5α,7α,11β-eudesman-12,6α-olide (10). A solution of 3α-hydroxy-4α,5α,7α,11β-eudesman-12,6α-olide (**6**) (5.7 g), freshly distilled 3,4-dihydro-2*H*-pyran (DHP) (4.7 g), and *p*-toluenesulfonic acid monohydrate (22 mg) in dry dichloromethane (45 ml) was stirred at 0 °C for 4 h. Diethyl ether (60 ml) was added and the solution was washed with aqueous sodium hydrogencarbonate and then saturated brine and dried over anhydrous sodium sulfate. The crude product was recrystallized from hexane-ethyl acetate to give **10** (4.2 g, 55% yield). Column chromatography of the mother liquid followed by recrystallization gave additional **10** (2.0 g, 26% yield).

Spectral data of **10**: Mp 158.5—159.0 °C, IR (KBr) 1772 cm^{-1}; ^{1}H NMR δ=1.04 (3H, s, 10-CH_3), 1.04 (3H, d, *J*=7.3 Hz, CH_3), 1.22 (3H, d, *J*=6.8 Hz, CH_3), 3.4—3.9 (3H, m, 3β-H and CH_2O), 3.98 (1H, dd, *J*=11.0 and 9.5 Hz, 6β-H), and 4.76 (1H, t, *J*=3.2 Hz, O-CH-O).

(11*S*)-3α-(Tetrahydro-2-pyranyloxy)-4α,5α,7α-eudesmane-6α,12-diol (11). To a solution of the lactone **10** (8.0 g) in dry diethyl ether (200 ml) was added lithium aluminium hydride (1.85 g) and the reaction mixture was stirred at room temperature for 4 h. An excess of lithium aluminium hydride was decomposed with ethyl acetate and water. Anhydrous sodium sulfate was added and the ethereal solu-

tion was evaporated to give an oily product, which was then purified by flash chromatography to give **11** (6.0 g, 75% yield), as a colorless solid, IR (Nujol) 3380 cm^{-1}; ^1H NMR δ=0.87 (3H, s, 10-CH_3), 0.89 (3H, d, J=6.8 Hz, CH_3), 0.99 (3H, d, J=7.3 Hz, CH_3), 3.4—4.0 (5H, m, 3β-H, 6β-H, 12-H, and O-CH_2), and 4.73 (1H, br s, O-CH-O). Found: m/z 340.2627. Calcd for $C_{20}H_{36}O_4$: M, 340.2614.

(11*S*)-3α,12-Dihydroxy-4α,5β,7α-eudesman-6-one (2). A mixture of the diol **11** (1.74 g), trityl chloride (TrCl) (1.60 g), 4-dimethylaminopyridine (31 mg,), triethylamine (1.28 ml) in dry dichloromethane (20 ml) was stirred at room temperature for 7 h. Trityl chloride (1.2 g) was then added and the reaction mixture was further stirred at room temperature overnight. Water was added and the product was extracted with diethyl ether. The crude alcohol **12** was oxidized as follows. To a solution of pyridine (7.1 ml) in dry dichloromethane (20 ml) was added chromium(VI) oxide (4.5 g) and the mixture was stirred at room temperature for 15 min. A solution of the crude alcohol **12** in dry dichloromethane (15 ml) was added and the reaction mixture was stirred at room temperature. The mixture was loaded onto a chromatographic column (silica gel 200 g) and eluted with hexane-ethyl acetate (3 : 1) to afford a mixture of triphenylmethanol and (11*S*)-3α-(tetrahydro-2-pyranyloxy)-12-trityloxy-4α,5α,7α-eudesman-6-one (**13**) (2.9 g); IR (neat) 1710 cm^{-1}. To a solution of the crude ketone **13** in methanol (25 ml) was added concentrated hydrochloric acid (1.6 ml) and the reaction mixture was stirred at room temperature. After neutralization with aqueous sodium hydrogencarbonate the solution was concentrated under reduced pressure. The product was extracted with ethyl acetate and purified by column chromatography (silica gel 15 g; eluent: hexane-ethyl acetate (1 : 1)) to give **2** (0.53 g; 40% yield from **11**); ^1H NMR δ=0.84 (3H, d, J=6.6 Hz, CH_3), 0.88 (3H, s, 10-CH_3), 0.92 (3H, d, J=7.1 Hz, CH_3), 2.54 (1H, ddd, J=13, 6, and 6 Hz, 7α-H), 3.4—3.6 (2H, m, 12-H), and 3.83 (1H, br s, 3-H). Diacetate of **2**. Found: m/z 338.2137. Calcd for $C_{19}H_{30}O_5$: M, 338.2093.

(11*S*)-7α-Eudesm-4-ene-6α,12-diol (14). A mixture of lithium aluminium hydride (52 mg) and 7α,11β-eudesm-4-en-12,6α-olide (**7**) (100 mg) in dry diethyl ether (10 ml) was stirred at room temperature for 1 h. Work-up as usual gave **14** quantitatively. The diol was recrystallized from acetone-diethyl ether to give colorless crystals; mp 168.9—170.3 °C; IR (KBr) 3400 and 3300 cm^{-1}; ^1H NMR δ=0.94 (3H, d, J=6.8 Hz, 11-CH_3), 1.06 (3H, s, 10-CH_3), 1.91 (3H, s, 4-CH_3), 3.53 (1H, dd, J=10.7 and 6.9 Hz, 12-H), 3.63 (1H, dd, J=10.7 and 6.0 Hz, 12-H), and 4.38 (1H, d, J=10.3 Hz, 6β-H); MS m/z (rel intensity) 238 (M^+; nil), 220 (M^+-H_2O; 24), 205 ($M^+-H_2O-CH_3$; 62), and 91 (100). Found: m/z 238.1889. Calcd for $C_{15}H_{26}O_2$: M, 238.1933.

(11*S*)-12-Hydroxy-7α-eudesm-4-en-6-one (3). A mixture of the allylic alcohol **14** (407 mg) and active manganese dioxide (4.16 g) in dichloromethane (70 ml) was stirred at room temperature for 1 h. After filtration the solvent was evaporated to give **3** (357 mg, 89% yield), which was then recrystallized from diethyl ether.

3: Mp 94.4—94.7 °C; IR (Nujol) 3510, 1663, and 1515 cm^{-1}; ^1H NMR δ=0.84 (3H, d, J=6.8 Hz, 11-CH_3), 0.88 (3H, s, 10-CH_3), 1.61 (3H, s, 4-CH_3), 3.40 (1H, dd, J=10.8 and 6.3 Hz, 12-H), and 3.52 (1H, dd, J=10.8 and 5.4 Hz, 12-H); MS m/z 236 (M^+; nil), 218 (M^+-H_2O; 38) and 203 ($M^+-H_2O-CH_3$; 100). Found: m/z 218.1678. Calcd for $C_{15}H_{22}O$: M−H_2O, 218.1671.

3,3-Ethylenedioxy-4β,5α,7α,11β-eudesman-12,6α-olide (15). A solution of 4β,5α,7α,11β-eudesman-12,6α-olide (**8**) (3.12 g), ethylene glycol (10.5 ml), *p*-toluenesulfonic acid monohydrate (170 mg) in benzene (160 ml) was heated under reflux and water was removed azeotropically using a Dean-Stark trap. The solution was washed successively with aqueous sodium hydrogencarbonate, water, and saturated brine, and then dried over anhydrous sodium sulfate. After evaporation of the solvent the residue was recrystallized from hexane-acetone to give **15** (3.24 g, 88% yield); mp 177.5—178.0 °C; IR (KBr) 1760 cm^{-1}; ^1H NMR δ=0.99 (3H, s, 10-CH_3), 1.04 (3H, d, J=6.6 Hz, CH_3), 1.19 (3H, d, J=6.8 Hz, CH_3), 3.81 (1H, dd, J=11.0 and 10.0 Hz, 6β-H), and 3.96 (4H, m, OCH_2CH_2O); MS m/z 294 (M^+; 3) and 99 (100).

(11*S*)-3,3-Ethylenedioxy-4β,5α,7α-eudesmane-6α,12-diol (16). To a suspension of lithium aluminium hydride (560 mg) in dry tetrahydrofuran (10 ml) was added a solution of the lactone **15** (2.45 g) in dry tetrahydrofuran (40 ml) and the reaction mixture was heated under reflux for 2.3 h. After working-up as described for **11** the product, obtained quantitatively, was recrystallized from methanol to give **16**, colorless plates; mp 155.0—155.5 °C; IR(Nujol) 3360 and 3280 cm^{-1}; ^1H NMR δ=0.86 (3H, s, 10-CH_3), 0.88 (3H, d, J=7.1 Hz, CH_3), 1.12 (3H, d, J=6.6 Hz, CH_3), 3.50 (3H, m, 6β-H and 12-H), and 3.90 (4H, m, OCH_2CH_2O); MS m/z 298 (M^+; 2), 280 (M^+-H_2O; 4), and 99 (100). Found: m/z 280.2065. Calcd for $C_{17}H_{28}O_3$: M−H_2O, 280.2038.

(11*S*)-12-Acetoxy-3,3-ethylenedioxy-4β,5α,7α-eudesman-6α-ol (17). Acetylation of the diol **16** (1.41 g) with acetic anhydride (6 ml) and pyridine (8 ml) at room temperature gave **17**, colorless solid, quantitatively.

Spectral data of **17**: IR (KBr) 3470 and 1740 cm^{-1}; ^1H NMR δ=0.87 (3H, s, 10-CH_3), 0.88 (3H, d, J=7 Hz, CH_3), 1.13 (3H, d, J=7 Hz, CH_3), 1.98 (1H, m), 2.05 (3H, s, $OCOCH_3$), 2.49 (1H, m, 11-H), 3.45 (1H, m, 6-H), and 3.95 (6H, m, 12-H and OCH_2CH_2O); MS m/z 340 (M^+; 0.2), 322 (M^+-H_2O; 0.2), and 99 (100). Found: m/z 340.2205. Calcd for $C_{19}H_{32}O_5$: M, 340.2250.

(11*S*)-12-Acetoxy-6α-hydroxy-4β,5α,7α-eudesman-3-one (18). A solution of the acetal **17** (1.55 g) and *p*-toluenesulfonic acid monohydrate (70 mg) in acetone (25 ml) was heated under reflux. Aqueous sodium hydrogencarbonate was added and the organic solvent was evaporated. Diethyl ether was added and the ethereal solution was washed with water and the saturated brine, and dried over anhydrous sodium sulfate. The crude product was chromatographed (eluent: hexane-ethyl acetate, 2 : 1) to give **18** (1.26 g, 93% yield).

Compound **18**: IR(KBr) 3470, 1740, and 1705 cm^{-1}; ^1H NMR δ=0.90 (3H, d, J=7 Hz, CH_3), 0.93 (3H, s, 10-CH_3), 1.33 (3H, J=7 Hz, CH_3), 2.06 (3H, s, $OCOCH_3$), 2.45 (3H, m, 2-H and 4-H), 3.47 (1H, m, 6β-H), and 3.98 (2H, m, 12-H). Found: m/z 296.1971. Calcd for $C_{17}H_{28}O_4$: M, 296.1988.

(11*S*)-12-Acetoxy-4β,5α,7α-eudesmane-3,6-dione (19). To a solution of **18** (790 mg) in acetone (30 ml) was added Jones reagent and the reaction was monitored by thin-layer chromatography. Work-up as usual gave **19** (706 mg, 90% yield), as an oil; IR (neat) 1735 and 1705 cm^{-1}; MS m/z 234 (M^+-CH_3COOH; 79), 219 ($M^+-CH_3COOH-CH_3$; 78), and 109 (100). Found: m/z 234.1629. Calcd for $C_{15}H_{22}O_2$: M−CH_3COOH, 234.1620.

(11*S*)-12-Hydroxy-4β,5α,7α-eudesmane-3,6-dione (4). To

a solution of **19** (210 mg) in methanol (10 ml) was added 5% aqueous potassium carbonate (2 ml) and the reaction mixture was allowed to stand at room temperature overnight. Evaporation of the solvent and extraction with diethyl ether gave a pale yellow oil (160 mg), which was then crystallized from carbon tetrachloride to give colorless prism; mp 95.0—96.0 °C; IR (KBr) 3420 and 1705 cm^{-1}; ^1H NMR δ=0.94 (3H, d, J=6.8 Hz, CH_3), 0.99 (3H, s, 10-CH_3), 0.99 (3H, d, J=6.4 Hz, CH_3), 2.67 (1H, m), 3.44 (1H, dd, J=10.7 and 6.7 Hz, 12-H), and 3.55 (1H, dd, J=10.7 and 4.9 Hz, 12-H); MS m/z 252 (M^+; nil), 234 (M^+-H_2O; 27), 219 ($M^+-H_2O-CH_3$; 70), and 69 (100). Found m/z 252.1741. Calcd for $C_{15}H_{24}O_3$: M, 252.1725.

(11*S*)-12-Hydroxy-7α-eudesm-4-ene-3,6-dione (5). A mixture of lithium aluminium hydride (503 mg) and 3-oxo-7α,11β-eudesm-4-en-12,6-olide **9** (502 mg) in diethyl ether (105 ml) was stirred at room temperature for 30 min. Work-up as usual yielded quantitatively a mixture of (11*S*)-7α-eudemane-3,6α,12-triols (**20**). A mixture of the triols **20** (268 mg), active manganese (IV) oxide (1.50 g) in dichloromethane (40 ml) was stirred at room temperature for 5 h. After filtration the solvent was evaporated to give an oily product. Chromatography of the oil on silica gel (15 g; eluent: hexane-ethyl acetate, 1 : 1) gave **5** (81 mg, 31% yield).

^1H NMR δ=0.92 (3H, d, J=6.8 Hz, 11-CH_3), 1.15 (3H, s, 10-CH_3), 1.73 (3H, s, 4-CH_3), 3.47 (1H, dd, J=11 and 9 Hz, 12-H), and 3.52 (1H, dd, J=11 and 6 Hz, 12-H); MS m/z 250 (M^+, 3), 232 (M^+-H_2O, 17), 217 ($M^+-H_2O-CH_3$, 42), and 164 (100). Found: m/z 250.1588. Calcd for $C_{15}H_{22}O_3$: M, 250.1569.

(11*S*)-3α,5ξ,12-Trihydroxy-4α,7ξ-eudesman-6-one (21). A solution of **2** (47 mg) and *p*-toluenesulfonic acid monohydrate (60 mg) in THF (2 ml)-H_2O (0.5 ml) was stirred at room temperature for 5 h. *m*-Chloroperoxybenzoic acid (40 mg) was then added and the mixture was stirred at room temperature overnight. After evaporation of the solvent water was added and the product was extracted with ethyl acetate. Column chromatography of the crude product (eluent: hexane-ethyl acetate 1 : 3) gave **21** (2 mg, 4% yield); ^1H NMR δ=1.17 (3H, d, J=7.3 Hz, 11-CH_3), 1.19 (3H, d, J=7.3 Hz, 4-CH_3), 1.21 (3H, s, 10-CH_3), 2.01 (1H, m, 11-H), 2.45 (1H, dq, J=5.5 and 7.5 Hz, 4-H), 3.72 (1H, dd, J=9.0 and 3.9 Hz, 12-H), and 4.23 (2H, m, 3β-H and 12-H).

Dehydration of 3 with *p*-Toluenesulfonic Acid in Benzene. A solution of the hydroxy ketone **3** (6 mg) in benzene (1 ml) was stirred in the presence of a catalytic amount of *p*-toluenesulfonic acid under nitrogen. The mixture was loaded onto a short column of silica gel and eluted with benzene to give an inseparable mixture of 6,12-epoxy-7α,11β-eudesma-3,5-diene (**22**) and 6,12-epoxy-11β-eudesma-4,6-diene (**23**) in a ratio of 2 : 3.

Spectral data of the mixture: IR (neat) 1663 and 1053 cm^{-1}; ^1H NMR δ=0.96 (3H, s, 10-CH_3), 1.08 (3H, d, J=6.8 Hz, 11-CH_3), 1.91 (3H, s, 4-CH_3), 3.76 (1H, t, J=8.5 Hz, 12-H), 4.43 (1H, t, J=8.5 Hz, 12-H), and 5.20 (1H, br s, 3-H) and **23**, δ=0.96 (3H, s, 10-CH_3), 1.05 (3H, d, J=6.4 Hz, 11-CH_3), 1.99 (3H, s, 4-CH_3), 3.49 (1H, dd, J=10 and 8 Hz, 12-H), and 4.20 (1H, t, J=8 Hz, 12-H).

Acid-Catalyzed Autoxidation of (11*S*)-12-Hydroxy-4β,5α,7α-eudesmane-3,6-dione (4). A solution of the hydroxy diketone **4** (53 mg) and *p*-toluenesulfonic acid monohydrate (64 mg) in benzene (3 ml) was stirred at room temperature overnight. The reaction mixture was chromatographed on silica gel [3 g; eluent: hexane-ethyl acetate (10 : 3)] to give 6,12-epoxy-11β-eudesma-4,6-dien-3-one (**24**) (28 mg, 57% yield); colorless oil, which was further purified by HPLC [RP-18 column; CH_3OH-H_2O (3 : 2)].

Spectral data of **24**: $[\alpha]_D^{18}$ +549° (*c* 0.72 $CHCl_3$); ^1H NMR δ=1.13 (3H, s, 10-CH_3), 1.15 (3H, d, J=6.8 Hz, 11-CH_3), 2.06 (3H, s, 4-CH_3), 3.85 (1H, t, J=8.7 Hz, 12-H), and 4.49 (1H, dd, J=9.8 and 8.7 Hz, 12-H); ^{13}C NMR δ=12.86 (15-C), 17.48 (13-C), 19.68, 21.24 (14-C), 33.86, 35.55 (10-C), 36.34, 37.89, 39.20 (11-C), 75.99 (12-C), 125.41, 128.36 (4-C), 146.93, 149.52, and 199.76 (3-C); MS m/z 232 (M^+; 44) and 217 (M^+-CH_3; 100). Found: m/z 232.1477. Calcd for $C_{15}H_{20}O_2$: M, 232.1463.

The reaction was also performed in benzene-d_6 in the presence of molecular sieves 4A under nitrogen and monitored by ^1H NMR spectroscopy. 6,12-Epoxy-4β,5α,11β-eudesm-5-en-3-one (**25**): ^1H NMR δ=0.68 (3H, d, J=6.3 Hz, 11-CH_3), 1.00 (3H, s, 10-CH_3), 1.55 (3H, d, J=7.3 Hz, 4-CH_3), 3.22 (1H, dd, J=10.4 and 8.2 Hz, 12-H), 3.73 (1H, q, J=7.3 Hz, 4-H), and 3.92 (1H, dd, J=8.2 and 7.7 Hz, 12-H) and 6,12-epoxy-4β,5α,11β-eudesm-6-en-3-one (**26**): ^1H NMR δ=0.75 (3H, s, 10-CH_3), 0.90 (3H, d, J=6.7 Hz, 11-CH_3), 1.50 (3H, d, J=6.6 Hz, 4-CH_3), 3.59 (1H, t, J=8.5 Hz, 12-H), and 4.24 (1H, dd, J=9.3 and 8.5 Hz, 12-H).

IR and MS spectra of the mixture **25** and **26**, an oil, are as follows: IR (neat) 1715 cm^{-1}; MS m/z 234 (M^+; 47), 232 (M^+-H_2; 59), 219 (M^+-CH_3; 100), and 217 ($M^+-H_2-CH_3$; 95). Found: 234.1637. Calcd for $C_{15}H_{22}O_2$: M, 234.1620.

Oxidation of 6,12-Epoxy-11β-eudesma-4,6-dien-3-one (24) with *m*-Chloroperoxybenzoic Acid in Tetrahydrofuran. A mixture of **24** (22 mg) and *m*-chloroperoxybenzoic acid (16 mg) in tetrahydrofuran (6 ml) was stirred at 0 °C for 3 h. *m*-Chloroperoxybenzoic acid (15 mg) was added. The mixture was further stirred for 1.5 h and then chromatographed on silica gel [2 g; eluent: hexane-ethyl acetate (3 : 2)] to give 3,7-dioxo-6,7-seco-11β-eudesm-4-en-6,12-olide **29** (2.5 mg, 10% yield) and (11*R*)-7α,12-dihydroxyeudesm-4-ene-3,6-dione (**28**) (14 mg, 54% yield). The lactone **29** was also obtained by the oxidation of **24** with *m*-chloroperoxybenzoic acid in dichloromethane in 56% yield.

29: IR (neat) 1735 and 1683 cm^{-1}; ^1H NMR δ=1.09 (3H, d, J=6.8 Hz, 11-CH_3), 1.36 (3H, s, 10-CH_3), 1.74 (3H, s, 4-CH_3), 2.35—2.75 (4H, m, 2-H and 8-H), 3.45 (1H, m, 11-H), 3.75 (1H, dd, J=10.5 and 9.6 Hz, 12-H), and 4.94 (1H, dd, J=10.5 and 7.1 Hz, 12-H); MS m/z 264 (M^+; 60) and 223 (100). Found: m/z 264.1305. Calcd for $C_{15}H_{20}O_4$: M, 264.1362.

28: IR (neat) 3400 and 1670 cm^{-1}; ^1H NMR δ=1.03 (3H, d, J=7.1 Hz, 11-CH_3), 1.15 (3H, s, 10-CH_3), 1.74 (3H, s, 4-CH_3), 3.72 (1H, dd, J=10.7 and 6.1 Hz, 12-H), and 4.11 (1H, dd, J=10.7 and 3.7 Hz); ^{13}C NMR δ=12.06, 12.44, 21.74, 31.11, 33.58, 35.10, 36.08, 37.05, 40.30, 65.73, 80.37, 132.29, 158.44, 199.20, and 206.83. Found: m/z 266.1517. Calcd for $C_{15}H_{22}O_4$: M, 266.1518.

(11*S*)-7β,12-Dihydroxyeudesm-4-ene-3,6-dione (31). A solution of **4** (80 mg) and *p*-toluenesulfonic acid monohydrate (8 mg) in benzene (15 ml) was heated under reflux for 8.5 h. After evaporation of the solvent the residue was chromatographed on silica gel (eluent: hexane-ethyl acetate (5 : 1)) to give **28** (9 mg, 10% yield) and **31** (5 mg, 5% yield).

Spectral data of **31**, an oil; IR (neat) 3480 and 1680 cm^{-1}; ^1H NMR δ=0.89 (3H, d, J=7.0 Hz, 11-CH_3), 1.21 (3H, s, 10-CH_3), 1.83 (3H, s, 4-CH_3), 3.68 (1H, dd, J=11.0 and 3.5 Hz, 12-H), and 4.01 (1H, dd, J=11.0 and 3.5 Hz, 12-H); ^{13}C NMR

δ=11.53, 12.61, 23.10, 32.49, 33.60, 35.55, 36.17, 37.47, 40.30, 63.44, 82.41, 134.46, 153.69, 198.43, and 208.00. Found: *m/z* 266.1514. Calcd for $C_{15}H_{22}O_4$: M, 266.1518.

6α,12-Epoxy-7α-hydroxy-6β-methoxy-11β-eudesm-4-en-3-one (30). The peracid oxidation of **24** (28 mg) was performed similarly in methanol to give **30** (17 mg, 51% yield).

Compound **30:** Colorless plates; mp 179.0—179.5 °C; UV (CH_3OH) 244 nm (ε 9100); IR (KBr) 3500, 1665, and 1600 cm^{-1}; ^1H NMR δ=1.02 (3H, d, *J*=7.1 Hz, 11-CH_3), 1.33 (3H, s, 10-CH_3), 2.07 (3H, s, 4-CH_3), 3.05 (3H, s, OCH_3), 3.55 (1H, t, *J*=8.3 Hz, 12-H), and 4.02 (1H, t, *J*=8.8 Hz, 12-H); MS *m/z* 280 (M^+; 23) and 163 (100). Found: *m/z* 280.1655. Calcd for $C_{16}H_{24}O_4$: M, 280.1674.

8-Hydroxy-2,5-octanedione. The hydroxy diketone was synthesized as follows. (i) Reduction of γ-valerolactone (1.3 g) with diisobutylaluminium hydride (1.5 mol dm^{-3}; 10 ml) in toluene (6 ml) gave a mixture of the corresponding lactols (diasteromeric ratio, 1 : 1.7; 706 mg, 53%). IR (neat) 3420 cm^{-1}; ^1H NMR [δ=1.22 (3H, d, *J*=6.3 Hz, CH_3), 4.35 (1H, m, CH-O), and 5.56 (1H, m, O-CH-O)] and [δ=1.35 (3H, d, *J*=6.1 Hz, CH_3), 4.13 (1H, m, CH-O), and 5.47 (1H, m, O-CH-O)]. (ii) Grignard reaction of the lactols (357 mg) with 3-butenylmagnesium bromide (prepared from 577 mg of magnesium and 1.4 g of 1-bromo-3-butene) in diethyl ether (13 ml) at room temperature gave 8-nonene-2,5-diol (295 mg, 53%): IR (neat) 3360, 3090, 1642, and 913 cm^{-1}. (iii) Jones oxidation of the diol (261 mg) in acetone (3 ml) at 0 °C gave 8-nonene-2,5-dione (208 mg, 77%): IR (neat) 3090, 1715, 1642, and 918 cm^{-1}; ^1H NMR δ=2.19 (3H, s, CH_3), 2.33 (2H, q, *J*=7.0 Hz, CH_2), 2.57 (2H, t, *J*=7.5 Hz, CH_2), 2.70 (4H, m, CH_2), 5.00 (2H, m, CH_2=), and 5.80 (1H, m, CH=). (iv) Acetalization of the diketone (176 mg) with ethylene glycol (1 ml) in the presence of *p*-toluenesulfonic acid monohydrate (10 mg) in benzene (15 ml) using a Dean-Stark trap gave 2,2 : 5,5-bis(ethylenedioxy)-8-nonene (251 mg, 91% yield). IR (neat) 3090 and 1642 cm^{-1}; MS *m/z* 242 (M^+; nil), 227 (M^+-CH_3; 5), 187 (61), 127 (100), 99(17), and 87 (84). (v) Ozonization of the olefin (128 mg) in methanol (3 ml) at −78 °C followed by reduction of the ozonide with sodium borohydride gave 2,2 : 5,5-bis(ethylenedioxy)-8-octanol (88 mg, 68%): IR (neat) 3460 cm^{-1}; ^1H NMR δ=1.31 (3H, s, CH_3), 1.73 (8H, m, CH_2), 3.64 (2H, t, *J*=5.8 Hz, CH_2OH), and 3.96 (8H, m, OCH_2CH_2O). (vi) Hydrolysis of the acetal in acetone in the presence of *p*-toluenesulfonic acid at room temperature gave 8-hydroxy-2,5-octanedione, but no autoxidation product was detected on thin-layer chromatography.

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