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An Easy Route to 11-Hydroxy-eudesmanolides. Synthesis of (±) Decipienin A.

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Abstract

The preparation of 11-hydroxy-eudesmanolides with the stereochemistry found in the Umbelliferae family of plants is described. The decalin system of the eudesmane skeleton is produced by the addition of 5-methyl-2-furyllithium to 3-ethoxycyclohex-2-enone and acidic treatment of the resulting adduct. The stereochemistry of the decalones obtained by this method has been corrected. The α-hydroxy-γ-lactone moiety is obtained by condensation of the appropriate decalone with methyl pyruvate and subsequent reduction under Luche conditions. The usefulness of this procedure has been proven in the synthesis of decipienin A.

Introduction

The structures and biological activities of sesquiterpene lactones are extremely diverse.[1] Most of them bear an *exo*-methylene conjugated to the carbonyl of the lactone group. Several authors consider this system responsible for the strong cytotoxic effect of this group of metabolites which limits their pharmacological use.[2] This system seems to block the metabolic cycle of the cell as a consequence of its behaviour as a Michael acceptor, particularly against L-cysteine residues (either free or protein-linked).[3]

There are several differences between sesquiterpenolides isolated from the Umbelliferae and Compositae families of plants, the latter being their main source. Usually, sesquiterpene lactones from Umbelliferae present a hydroxy or acyloxy group α to the carbonyl group of the lactone, instead of the exocyclic double bond (Fig. 1). We are interested in checking the biological activity of these lactones. This system could be considered as a formal precursor of the *exo*-methylene γ-lactone, so the unsaturated system could be released in small quantities and in this way the cytotoxic effect would be attenuated.

The synthesis of eudesmanolides has been approached in many different ways. Most of these syntheses involve the construction of decalin rings using reactions such as Robinson annulation, Diels-Alder cycloaddition, oxy-Cope or anionic oxy-Cope rearrangement or photochemical [2+2] cycloaddition with subsequent ring expansion.[4]

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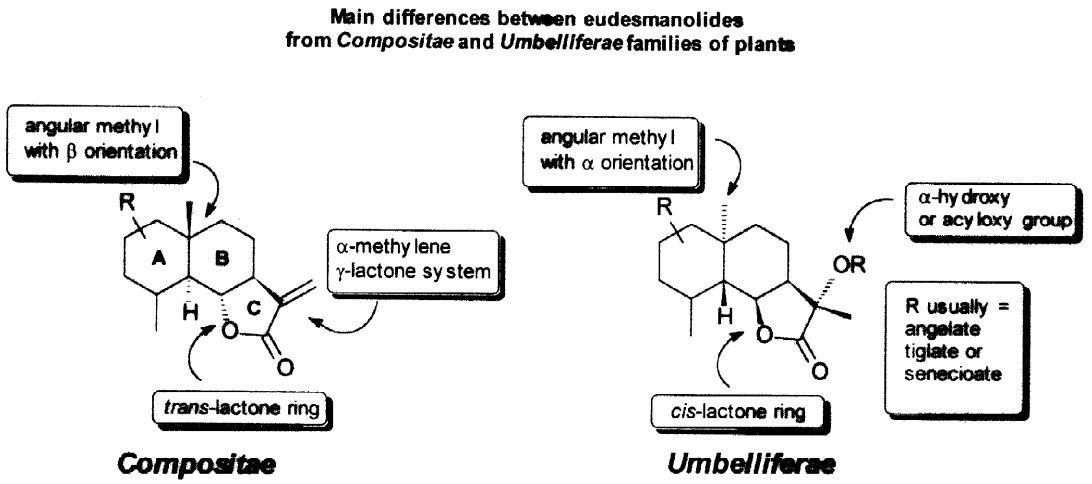
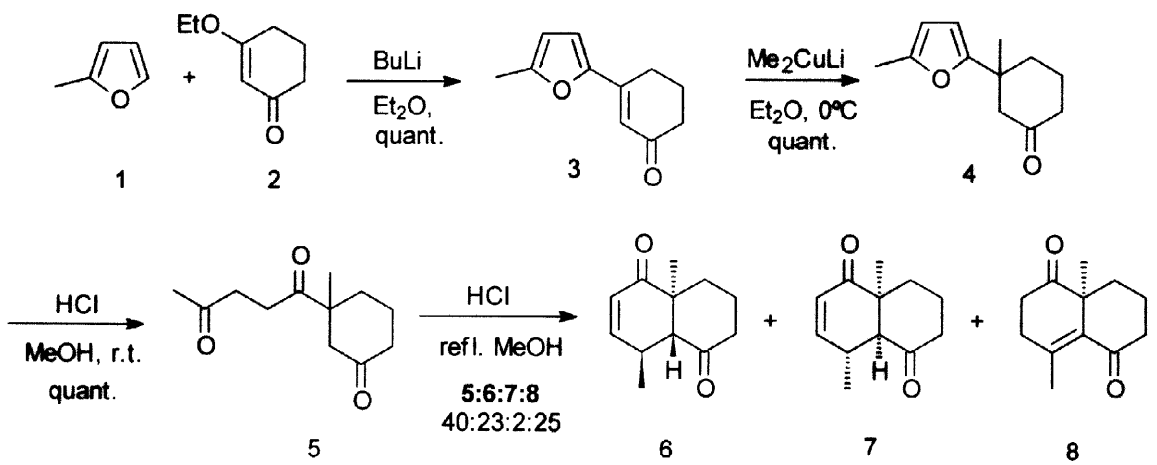


Fig. 1

Synthesis of 11-hydroxyeudesmanolides.

As a consequence of our ongoing project on the synthesis of sesquiterpene lactones from the Umbelliferae family of plants, our attention was drawn to a paper by Kametani *et al.* which describes the construction of 1,6-dioxygenated decalins by using a 2-methylfuran ring as a synthon to build the A ring in such systems.[5] Our survey of the literature convinced us that functionalization at C-1 is not easy and usually involves many steps. Therefore we decided to explore the possibilities of this approach as a method of access to eudesmanolides with diverse functionalization in the A ring.



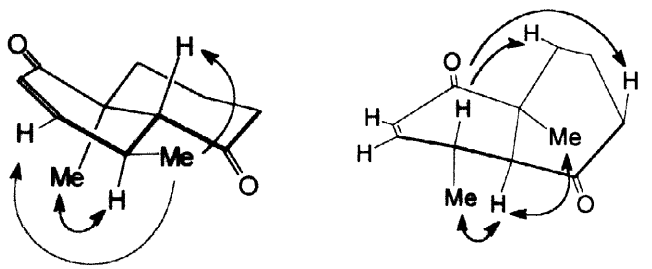
Scheme 1

The strategy of synthesis began (Scheme 1) with 2-methylfuran, **1**, which was lithiated with n-BuLi and the resulting anion treated with 3-ethoxycyclohex-2-enone, **2**, yielding the α,β-unsaturated ketone **3**. In the previous work by Kametani, the introduction of the methyl group was carried out with MeCu in the presence of Bu_3P. The drawback of this procedure was the difficulty of removing the phosphine. Changing to Ph_3P or using acid catalysis ($BF_3{\cdot}Et_2O$) did not solve this problem nor improve the yield. Quantitative yields were eventually obtained by using Me_2CuLi instead of the MeCu/phosphine system.

The furan opening proceeded in quantitative yield. This reaction was performed by treatment of adduct **4** with conc. HCl in MeOH at room temperature, giving the triketone **5**.

For the cyclization of **5**, we tried several conditions. Unfortunately, most of these trials led back to furan **4** as a result of ring closure. Refluxing **5** with a 1:1 HCl:MeOH mixture produced an equilibrium mixture of **5**:**6**:**7**:**8** in a 40:23:2:25 ratio. Removal of any of the components of the above mixture by chromatography and treatment of the remaining components in the same conditions led to a new mixture with the same ratio. In this way, we were able to get enough of each of the components to continue our synthetic route.

At this stage, we assumed the stereochemistry to be that assigned in the original paper, but the results obtained from this point onwards were not consistent. These ambiguous results prompted us to reinvestigate the stereochemistry of the decalones **6** and **7**. The observed n.O.e.s are displayed in the Fig. 2.[6]



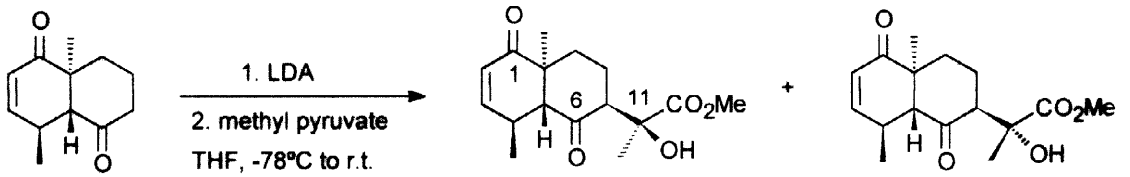
6 **7**

Observed n.O.e.s for decalones 6 and 7

Fig. 2

With the decalone **6** thus obtained, the next step was the construction of the α-hydroxy-γ-lactone ring. Despite the great number of syntheses of sesquiterpenolides published, to the best of our knowledge, only two approaches have dealt with 11-hydroxy-sesquiterpenolides.[7,8] Usually, α-hydroxylation of a carbonyl group is performed by enolate formation and trapping of the enolate with an oxygenated electrophile. The more common electrophiles used include dimethyldioxirane (DMD),[9] *N*-sulfonyloxaziridines,[10] bis(trimethylsilyl) peroxide (BTSP),[11] the molybdenum peroxide reagent MoO_5·Py·HMPA[12] or molecular oxygen.[7]

Our approach involves a different strategy. We have used methyl pyruvate as a synthon to achieve this functionalization. Thus, the lithium enolate of decalone **6** was treated with methyl pyruvate at –78°C, affording a 1:1 mixture of epimers **10a** and **10b** (Scheme 2). The stereochemistry at C-11 was confirmed in the subsequent steps by n.O.e. measurements.

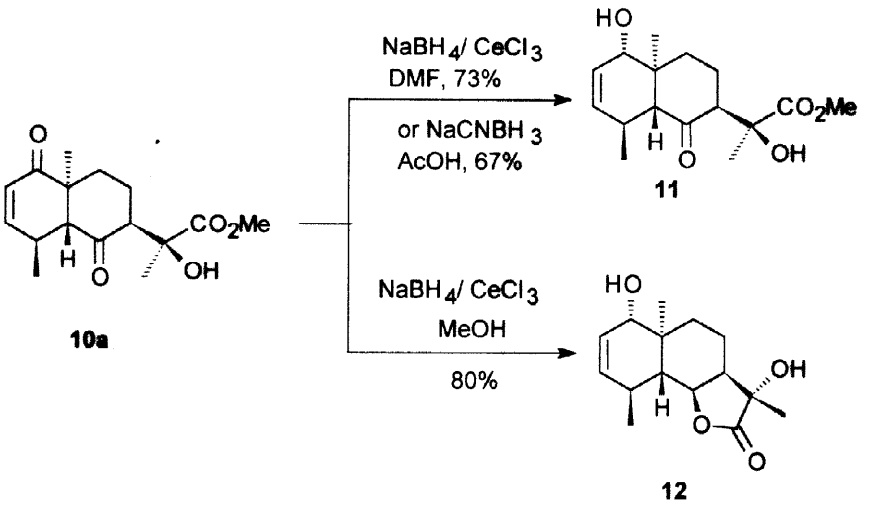


6 **10a**, 49% **10b**, 49%

Scheme 2

The next step was the reduction of the C-6 carbonyl group of **10a** and the displacement of the methoxy group of the ester by the resulting alkoxide. This step revealed itself as the most complex of the entire route, for several reasons. First, the carbonyl at C-6 is very hindered. This fact precluded the possibility of using bulky reducing agents such as DIBAL that would have

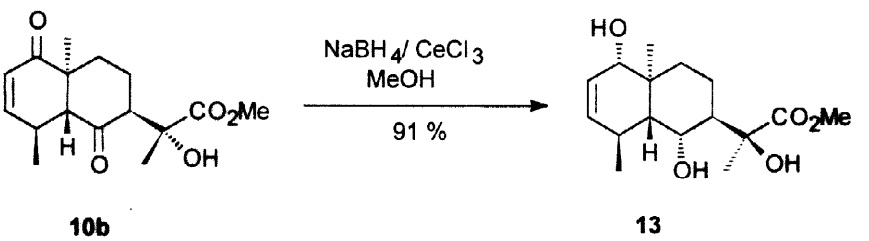
ensured the correct stereochemistry of the lactone ring (*cis*). Second, compound **10a** is very prone to undergo a retroaldol reaction. And third, we wanted to avoid the epimerization at C-7. These three reasons, together with the presence of an α,β-unsaturated ketone in the A ring, led us to choose the reduction with $NaBH_4$ under Luche conditions[13] as the best choice to obtain the 11-hydroxy-γ-lactone (Scheme 3).



Scheme 3

It is interesting to note that the presence of $CeCl_3$ in this process changes the orientation in the hydride attack.[14] Also, the solvent plays an important role. When the reduction was carried out in DMF, no reduction in C-6 was observed. The same result was obtained when $NaCNBH_3$ was used.

The behaviour of the two epimers **10a** and **10b** is different, each showing a different orientation in the hydride attack under the same conditions (Scheme 4).



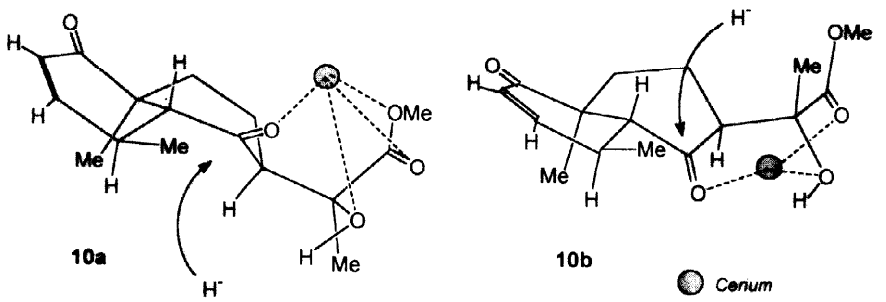
Scheme 4

We think that in **10a**, the cerium could coordinate with several of the oxygen atoms from the upper face of the molecule, the carbonyl being attacked from the lower face, yielding the lactone. In the reduction of **10b** such coordination occurs on the lower face, so the axial alcohol is produced (Fig. 3). The stereochemistry of the hydroxyl group on C-11 has been revealed as a determining factor in the orientation of the reduction. This behavior has been described before in the reduction of hindered diphenylphosphinoyl ketones[15] and some enones.[16]

Synthesis of Decipienin A.

Lactone **12** made functionalization possible at any position of the A ring. We decided that decipienin A, **19**, would be an excellent target to check this methodology. Decipienin A is an eudesmanolide isolated from *Melanoselinum decipiens* which displays the typical

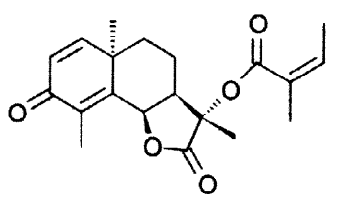
stereostructure of the eudesmanolides from Umbelliferae. It was first described by Galindo *et al.*[17] and its stereochemistry was corrected in 1986 by Holub *et al.*[18] The stereochemistry assigned by Holub is confirmed by our synthesis.



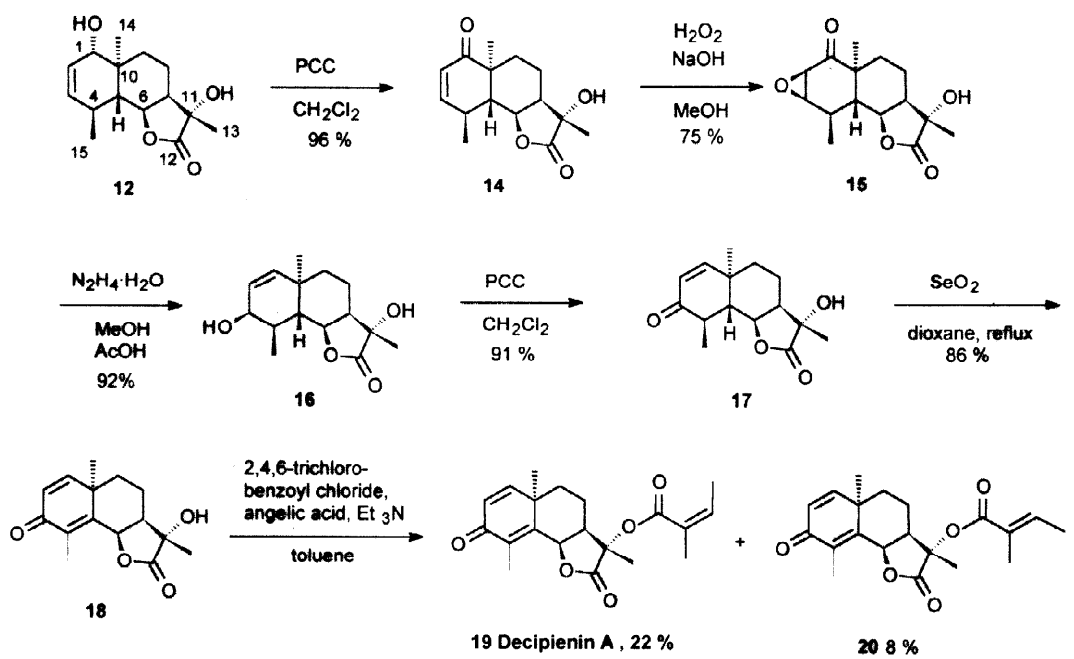
Orientation of the hydride attack in the presence of $CeCl_3$

Fig.3

To this end, lactone **12** was oxidized with PCC to give the enone lactone **14** which was treated with hydrogen peroxide in basic media, affording the epoxy ketone **15** (Scheme 5). Compound **15** underwent a Wharton rearrangement under treatment with hydrazine hydrate, producing the allylic alcohol **16** with a high overall yield. Subsequent oxidation with PCC yielded the α,β-unsaturated ketone **17** which was dehydrogenated with selenium dioxide in refluxing dioxane to give the dienone **18**. Lastly, esterification of the tertiary alcohol in C-11 was achieved using the procedure described by Greene *et al.*, using angelic acid and 2,4,6-trichlorobenzoyl chloride.[19] Any other attempt to improve the yield of the esterification led to a higher ratio of the tigloyl ester.[20] In this way, decipienin A, **19**, was obtained in a total of 12 steps. Its spectra were fully consistent with those of the



19 Decipienin A



Scheme 5

natural product, confirming the assumptions made by Holub about its stereochemistry.

Conclusions

An easy way to construct 11-hydroxy-eudesmanolides, typical of plants of the Umbelliferae family, is achieved via a condensation of the appropriate decalone with methyl pyruvate. Such decalones are obtained following the improved procedure developed by Kametani *et al.* which uses a 2-methylfuran and 3-ethoxycyclohex-2-enone as starting materials to build the A-ring. As a means of proving the utility of this methodology, Decipienin A has been synthesized. Currently, we are working on the enantioselective synthesis of these kinds of metabolites in order to assess their biological activities.

Experimental

General. All non-aqueous reactions were carried out under nitrogen atmosphere. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe or stainless steel cannula. Reactions were monitored using TLC on commercial silica 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 silica gel column (LiChrosorb Si 60, 7 μm particle size, 1×25 cm). THF, dioxane, diethyl ether, toluene and triethylamine were distilled from sodium metal under nitrogen. Dichloromethane was 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 Unity 400 using $CDCl_3$ as a solvent unless otherwise noted. Spectra were referenced internally to residual protio solvent signals. Data for ^1H 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 GCMS or in a VG Autospec-Q.

Condensation of 2-methylfuran 1 and 3-ethoxycyclohex-2-enone 2.

To a solution of 2-methylfuran **1** (11.58 ml, 128.5 mmol) in dry Et_2O (100 ml) at 0 °C was added a 10 M solution in hexanes of *t*-butyllithium (12.85 ml, 128.5 mmol). After addition, the cold bath was removed and the reaction was heated at 40 °C for 30 min. The solution was cooled down to 0 °C and 3-ethoxycyclohex-2-enone **2** (15.58 ml, 107.1 mmol) was added dropwise. The reaction was stirred at 0 °C for 2 h, after which time the solution was poured into saturated NH_4Cl (100 ml). The aqueous layer was separated and extracted with Et_2O (3 × 75 ml). The combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation yielded **3** (18.65 g, quantitative yield) as orange crystals. For analytical purposes, a sample was recrystallized from EtOAc/hexanes.

3-(4'-Methylfuranyl)cyclohex-2-enone 3. Orange crystals. m.p. (EtOAc/hexanes) 65.8-67.6 °C. IR (thin film) ν 2932, 2898, 2866, 1628, 1598, 1512, 1420, 1318, 1181, 1151, 767. HRMS calcd. for $C_{11}H_{12}O_2$ 176.0837, found 176.0826. MS *m/z* (rel. int.): 178 $[M]^+$ (1.9), 176 $[M-2]^+$ (70.3), 148 $[M-CH_2O]^+$ (100), 120 $[C_8H_8O]^+$ (60.5), 105 (25.4), 77 (12.6). ^1H-NMR δ 6.63 (1H, d, *J* = 3.4 Hz, H-2'), 6.40 (1H, s, H-2), 6.10 (1H, dq, *J* = 3.4, 1.0 Hz, H-3'), 2.59 (2H, t, *J* = 5.9 Hz, 2H-4), 2.43 (2H, t, *J* = 6.6 Hz, 2H-6), 2.33 (3H, br s, 3H-5'), 2.07 (2H, dq, *J* = 6.6, 5.9 Hz,

2H-5). ^{13}C-NMR δ 199.5 (C-1), 155.8 (C-3)*, 150.5 (C-1')*, 147.2 (C-4')*, 119.6 (C-2), 114.1 (C-2'), 108.9 (C-3'), 37.5 (C-6), 25.2 (C-4), 22.4 (C-5), 13.9 (C-5'). * interchangeable

Methylation of 3 with Me_2CuLi.

To a suspension of copper(I) iodide (2.257 g, 119 mmol) in Et_2O (400 mL) at 0 °C was added dropwise a 1.5 M solution of MeLi·LiBr in ether (158.4 mL, 238 mmol). The mixture was stirred at 0 °C for 30 min and then a solution of **3** (16.68 g, 91.4 mmol) in Et_2O (150 mL) was added dropwise. A yellow precipitate was formed. After 1.5 h, the reaction was poured onto iced saturated aqueous NH_4Cl (200 mL). The aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed by rotary evaporation, yielding compound **4** as a yellow oil (17.5 g, quantitative yield). This product was used in the next step without further purification.

3-Methyl-3-(4'-methylfuran-1'-yl)cyclohexanone 4. Yellow oil. IR (thin film) ν 2955, 2940, 2867, 1700, 1449, 1229, 1015, 767. HRMS calcd. for $C_{12}H_{16}O_2$ 192.1150, found 192.1126. MS *m/z* (rel. int.): 192 $[M]^+$ (67.2), 177 $[M\text{-}CH_3]^+$ (60.1), 149 $[M\text{-}CH_3\text{-}CO]^+$ (62.1), 135 $[C_9H_{11}O]^+$ (74.3), 121 $[C_8H_9O]^+$ (100), 107 (56.5), 91 (45.9), 77 (46.4). ^{1}H-NMR δ 5.83 (1H, d, *J* = 3.1 Hz, H-2'), 5.79 (1H, dq, *J* = 3.1, 1.0 Hz, H-3'), 2.69 (1H, ddd, *J* = 14.3, 1.6, 1.6 Hz, H-2α), 2.28 (1H, d, *J* = 14.3 Hz, H-2β), 2.20 (3H, d, *J* = 1.0 Hz, 3H-5'), 2.30-2.10 (3H, m, H-4α, 2H-6), 1.79 (1H, m, H-5β), 1.68 (1H, ddd, *J* = 12.7, 9.5, 3.5 Hz, H-4β), 1.57 (1H, ddddd, *J* = 12.8, 9.5, 9.5, 5.6, 3.4 Hz, H-5α), 1.28 (3H, s, 3H-7). ^{13}C-NMR δ 210.6 (C-1), 157.9 (C-4')*, 150.7(C-1')*, 105.6 (C-3')[a], 105.5 (C-2')[a], 51.8 (C-2), 40.6 (C-6)[b], 40.4 (C-3), 35.9 (C-4)[b], 27.1 (C-5'), 22.0 (C-5)[b], 13.4 (C-7). *, a, b interchangeable.

Acid treatment of methylfuran 4.

A solution of methylfuran **4** (10.2 g, 53.1 mmol) in a 1:1 mixture of conc. HCl/MeOH (250 mL) was stirred at r.t. for 3 h. After this time, TLC indicated that the conversion to compound **5** was complete. The mixture was then heated to reflux for 12 h. The solution was diluted with water (500 mL) and the methanol was removed in the rotary evaporator. The reaction was then extracted with CH_2Cl_2 (3 × 250 mL). The organic layers were washed with aq. saturated $NaHCO_3$ (3 × 250 mL) and brine (3 × 250 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, providing a mixture of compounds **5**, **6**, **7** and **8**. Purification by flash chromatography (silica gel, EtOAc/hexanes 1:9) afforded 2.565 g of decalone **6** (23 %), 2.787 g of decalone **8** (25 %) , 0.223 g of decalone **7** (2 %) and 4.46 g of compound **5** (40 %).

3-Methyl-3-(1',4'-dioxopentyl)cyclohexanone 5. Brown-yellow oil. IR (thin film) ν 2939, 2875, 1712, 1606, 1461, 1454, 1424, 1414, 1360, 1227, 1196, 1166, 1086, 1031, 1011, 756. HRMS calcd. for $C_{10}H_{15}O_2$ $[M\text{-}COCH_3]^+$ 167.1072, found 167.1062. MS *m/z* (rel. int.): 210 $[M]^+$ (2.7), 192 $[M - H_2O]^+$ (19.4), 150 $[C_9H_{10}O_2]^+$ (13.1), 135 $[C_9H_{10}O_2 - CH_3]^+$ (10.6), 111 (72.4), 97 $[C_5H_5O_2]^+$ (100), 55 (45.2). ^{1}H-NMR δ 2.80-2.50 (4H, m), 2.3-2.1 (2H, m), 2.08 (3H, s, 3H-5'), 2.05-1.5 (6H, m), 1.18 (3H, s, 3H-7). ^{13}C-NMR δ 211.8 (C-1)*, 209.5 (C-1')*, 206.9 (C-4')*, 51.6 (C-3), 49.2, 39.9, 36.5, 33.4, 30.4, 29.7 (C-5'), 23.5 (C-7), 21.5. * interchangeable.

Decalone 6. Colorless crystals. m.p. (CH_2Cl_2) 80.0-81.5 °C. IR (thin film) ν 2976, 2938, 1723, 1681, 1636, 1259, 1086, 799. HRMS calcd. for $C_{12}H_{16}O_2$ 192.1150, found 192.1157. MS *m/z* (rel. int.): 192 $[M]^+$ (36.9), 177 $[M - CH_3]^+$ (4.3), 174 $[M - H_2O]^+$ (3.7), 159 $[M - CH_3 - H_2O]^+$ (5.1), 156 $[M - 2 \times H_2O]^+$ (0.2), 147 $[M - C_2H_5O]^+$ (70.5), 82 (100), 77 (20.8). ^{1}H-NMR δ 6.60 (1H, dd, *J* = 10.2, 2.1 Hz, H-3), 5.84 (1H, dd, *J* = 10.2, 2.7 Hz, H-2), 2.88 (1H, dqdd, *J* = 9.9, 7.0, 2.7, 2.1 Hz, H-4), 2.64 (1H, d, *J* = 9.9 Hz, H-5), 2.40-2.20 (2H, m, 2H-7), 2.20-1.70 (4H,

m, 2H-8, 2H-9), 1.10 (3H, d, J = 7.0 Hz, 3H-12), 0.99 (3H, s, 3H-11). ^{13}C-NMR δ 209.7 (C-6), 201.2 (C-1), 153.3 (C-3), 125.5 (C-2), 61.9 (C-5), 49.7 (C-10), 41.8 (C-7), 31.6 (C-9), 28.3 (C-4), 22.4 (C-8), 19.5 (C-12), 17.2 (C-11).

Decalone 7. Yellow oil. IR (thin film) ν 2964, 2937, 2875, 1709, 1674, 1457, 1380, 1265, 1235, 1189, 1147, 1098, 819. HRMS calcd. for $C_{12}H_{16}O_2$ 192.1150, found 192.1127. MS *m/z* (rel. int.): 192 $[M]^+$ (22.0), 177 $[M - CH_3]^+$ (4.8), 174 $[M - H_2O]^+$ (1.6), 159 $[M - CH_3 - H_2O]^+$ (2.4), 147 $[C_{10}H_{11}O]^+$ (24.7), 82 (100), 77 (17.3). ^{1}H-NMR δ 6.66 (1H, dd, J = 10.2, 2.4 Hz, H-3), 5.94 (1H, dd, J = 10.2, 2.7 Hz, H-2), 2.93 (1H, dqdd, J = 9.9, 7.2, 2.7, 2.4 Hz, H-4), 2.50 (1H, ddd. J = 14.6, 11.8, 7.5 Hz, H-7β), 2.30 (1H, dddd, J = 14.6, 3.4, 3.4, 1.5 Hz, H-7α), 2.29 (1H, d, J =9.9 Hz, H-5), 2.05 (1H, ddd, J = 13.5, 13.5, 4.9 Hz, H-9β), 1.97-1.88 (2H, m, 2H-8), 1.45 (1H, dddd, J = 13.5, 3.8, 3.8, 1.5 Hz, H-9α), 1.12 (3H, s, 3H-11), 1.09 (3H, d, J = 7.2 Hz, 3H-12). ^{13}C-NMR δ 210.6 (C-6), 200.9 (C-1), 152.0 (C-3), 127.0 (C-2), 62.9 (C-5), 47.6 (C-10), 37.5 (C-7), 30.8 (C-4), 29.6 (C-9), 21.3 (C-8), 21.3 (C-12), 18.7 (C-11).

Decalone 8. Colorless crystals. m.p. (EtOAc/hexanes): 69.2-71.5 °C. IR (thin film) ν 2973, 2941, 1721, 1693, 1453, 1268, 1217, 1101, 803. HRMS calcd. for $C_{12}H_{16}O_2$ 192.1150, found 192.1161. MS *m/z* (rel. int.): 192 $[M]^+$ (36.5), 177 $[M - CH_3]^+$ (8.6), 174 $[M - H_2O]^+$ (1.4), 164 $[M - CO]^+$ (39.7), 149 $[M - CO - CH_3]^+$ (100), 135 $[C_8H_7O_2]^+$ (74.9), 107 $[C_7H_7O]^+$ (19.8), 79 (36.4). ^{1}H-NMR δ 2.75-2.20 (6H, m), 1.98-1.76 (4H, m), 1.87 (3H, br s, 3H-12), 1.17 (3H, s, 3H-11). ^{13}C-NMR δ 213.1 (C-1), 204.6 (C-6), 138.3 (C-5)*, 137.9 (C-4)*, 49.6 (C-10), 42.4 (C-2)[a], 34.9 (C-7)[a], 32.7 (C-9)[a], 32.4 (C-3)[a], 24.1 (C-12), 20.8 (C-11), 20.1 (C-8).

*, [a] interchangeables.

Condensation of decalone 6 with methyl pyruvate.

To a solution of decalone **6** (1.823 g, 9.50 mmol) in dry THF (150 mL) was added dropwise a 2N LDA solution in hexanes (5.2 mL, 10.4 mmol) at –78 °C. 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 and was then allowed to reach r.t. The reaction was poured onto saturated aq. NH_4Cl (150 mL). The mixture was 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 yielding 2.792 g (98%) of a 1:1 mixture of epimers **10a** and **10b**. Purification was carried out by semipreparative HPLC (EtOAc/hexanes 1:2).[21]

Hydroxy keto ester 10a. Colorless crystals. m.p. (EtOAc/hexanes) 89.1-90.2°C. IR (thin film) ν 3482, 2960, 2874, 1735, 1701, 1678, 1620, 1452, 1377, 1256, 1204, 974. HRMS calcd. for $C_{14}H_{19}O_3$ $[M - CO_2CH_3]^+$ 235.1334, found 235.1334. MS *m/z* (rel. int.): 294 $[M]^+$ (13.7), 235 $[M - CO_2CH_3]^+$ (78.4), 217 $[M - CO_2CH_3 - H_2O]^+$ (35.0), 192 $[M - C_4H_6O_3]^+$ (41.7), 175 $[M - C_4H_5O_3 - H_2O]^+$ (87.7), 82 (100), 77 (35.4), 55 (57.9). ^{1}H-NMR δ 6.62 (1H, dd, J = 10.1, 2.2 Hz, H-3), 5.85 (1H, dd, J = 10.1, 2.7 Hz, H-2), 3.80 (3H, s, OC<u>H</u>$_3$), 3.69 (1H, s, O<u>H</u>), 3.26 (1H, d, J = 9.5 Hz, H-5), 2.91 (1H, dqdd, J = 9.5, 6.8, 2.7, 2.2 Hz, H-4), 2.65 (1H, dd, J = 7.1, 3.2 Hz, H-7), 2.33 (1H, ddd, J = 14.8, 12.8, 5.4 Hz, H-9β), 1.88 (1H, dddd, J = 15.2, 7.1, 5.6, 5.4 Hz, H-8α), 1.73 (1H, dddd, J =15.2, 12.8, 4.7, 3.2 Hz, H-8β), 1.72 (1H, ddd, J = 14.8, 5.6, 4.7 Hz, H-9α), 1.31 (3H, s, 3H-13), 1.14 (3H, d, J = 6.8 Hz, 3H-15), 0.98 (3H, s, 3H-14). ^{13}C-NMR δ 211.0 (C-6), 202.2 (C-1), 176.2 (<u>C</u>O$_2$CH$_3$), 153.4 (C-3), 125.6 (C-2), 76.6 (C-11), 60.3 (C-5), 54.6 (C-7), 53.4 (CO$_2$<u>C</u>H$_3$), 48.1 (C-10), 28.8 (C-9), 28.0 (C-4), 25.2 (C-13), 23.3 (C-8), 19.2 (C-15), 18.9 (C-14).

Hydroxy keto ester 10b. Colorless crystals. m.p. (EtOAc/hexanes) 113.8-115.0 °C. IR (thin film) ν 3475, 2958, 2883, 1732, 1693, 1660, 1451, 1430, 1392, 1376, 1256, 1208, 971. HRMS calcd. for $C_{12}H_{16}O_2$ [M – $C_4H_6O_3$]$^+$ 192.1150, found 192.1166. 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). ^{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, $CO_2C\underline{H}_3$), 3.33 (1H, s, O<u>H</u>), 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 ($CO_2\underline{C}H_3$), 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).

Reduction of ester 10a with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ in DMF.

A solution of ester **10a** (65 mg, 0.22 mmol) and $CeCl_3{\cdot}7H_2O$ (162 mg, 0.44 mmol) in DMF (2 mL) was stirred for 30 min at r.t. Then $NaBH_4$ (17 mg, 0.45 mmol) was added. After 1 h, the reaction mixture was neutralized with aq. 1N HCl. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 25 mL). The organic layer was washed with brine (3 × 25 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Purification by flash chromatography (EtOAc/hexanes, 1:2) afforded 48 mg (73 % yield) of alcohol **11**.

Alcohol 11. Colorless oil. IR (thin film) ν 3461, 3445, 2953, 2938, 2874, 1770, 1734, 1671, 1258, 1208, 1165, 1107, 735. HRMS calcd. for $C_{16}H_{24}O_5$ 296.1624, found 296.1623. ^{1}H-NMR δ 5.54 (1H, dt, *J* = 10.1, 2.3 Hz, H-2), 5.40 (1H, ddd, *J* = 10.1, 2.3, 1.6 Hz, H-3), 4.19 (1H, m, H-1), 3.79 (3H, s, $CO_2C\underline{H}_3$), 2.70 (1H, d, *J* = 9.2 Hz, H-5), 2.60 (1H, dd, *J* = 6.4, 4.8 Hz, H-7), 2.54 (1H, m, H-4), 2.11 (1H, m, H-9α), 1.82-1.72 (2H, m, 2H-8), 1.57 (1H, dt, *J* = 14.0, 5.2 Hz, H-9β), 1.33 (3H, s, 3H-13), 0.96 (3H, d, *J* = 6.8 Hz, 3H-15), 0.76 (3H, s, 3H-14). ^{13}C-NMR δ 212.2 (C-6), 175.6 (C-12), 134.1 (C-2), 127.6 (C-3), 76.6 (C-11), 76.2 (C-1), 59.0 (C-5), 55.1 (C-7), 53.3 ($CO_2\underline{C}H_3$), 35.0 (C-10), 33.0 (C-9), 27.2 (C-4), 25.2 (C-13), 23.6 (C-8), 19.8 (C-15), 14.1 (C-14).

Reduction of ester 10a with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ in MeOH

A solution of ester **10a** (235 mg, 0.80 mmol) and $CeCl_3{\cdot}7H_2O$ (596 mg, 1.60 mmol) in MeOH (10 mL) was stirred for 30 min at r.t. Then $NaBH_4$ (60 mg, 1.59 mmol) was added. After 1 h, the mixture of reaction was neutralized with aq. 1N HCl. The mixture was filtered and extracted with EtOAc (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (EtOAc/hexanes 2:1) afforded 179 mg (80% yield) of lactone **12**.

1α,11α-Dihydroxy-4αH,5βH,6αH,7αH,10αMe-eudesman-2,3-en-6,12-olide 12. Colorless crystals. m.p. (MeOH) 69.5-71.8 °C. IR (thin film) ν 3452, 3437, 2947, 2880, 1767, 1675, 1464, 1392, 1146, 1102, 974. HRMS calcd. for $C_{15}H_{22}O_4$ 266.1518, found 266.1499. ^{1}H-NMR δ 5.42 (1H, dt, *J* = 10.1, 2.0 Hz, H-2), 5.37 (1H, ddd, *J* = 10.1, 2.0, 1.3 Hz, H-3), 4.59 (1H, dd, *J* = 9.4, 8.1 Hz, H-6), 3.81 (1H, m, H-1), 3.67 (1H, s, O<u>H</u>), 2.55 (1H, ddd, *J* = 13.6, 8.1, 5.6 Hz, H-7), 2.10 (1H, m, H-4), 1.80-1.60 (3H, m, 2H-8, H-9β), 1.40 (1H, m, H-9α), 1.32 (3H, s, 3H-13), 1.21 (1H, t, *J* = 9.5 Hz, H-5), 1.08 (3H, d, *J* = 6.8 Hz, 3H-15), 0.82 (3H, s, 3H-14). ^{13}C-

NMR δ 180.1 (C-12), 134.9 (C-2), 129.9 (C-3), 83.3 (C-6), 77.5 (C-1), 75.5 (C-11), 49.0 (C-5), 45.5 (C-7), 39.0 (C-10), 36.7 (C-4), 34.5 (C-9), 21.8 (C-13), 21.3 (C-15), 19.1 (C-8), 13.9 (C-14).

Reduction of ester 10b with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$.

A solution of ester **10b** (139 mg, 0.47 mmol) and $CeCl_3 \cdot 7H_2O$ (352 mg, 0.95 mmol) in MeOH (10 mL) was stirred for 30 min at r.t. Then, $NaBH_4$ (36 mg, 0.95 mmol) was added. After 1 h, the mixture of reaction was neutralized with aq. 1N HCl. The mixture was filtered and extracted with EtOAc (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and removed under reduced pressure. Purification by flash chromatography (EtOAc/hexanes, 2:1) afforded 128 mg (91% yield) of triol **13**.

Trihydroxy ester 13. Colorless oil. IR (thin film) ν 3471, 3456, 3444, 3015, 2952, 2874, 1724, 1655, 1455, 1438, 1397, 1373, 1256, 1218, 1200, 1176, 1144, 1105, 1086, 1055, 972. HRMS calcd. for $C_{16}H_{26}O_5$ 298.1780, found 298.1778. ^{1}H-NMR δ 5.55 (1H, dt, J = 10.0, 2.2 Hz, H-2), 5.41 (1H, ddd, J = 10.0, 2.2, 1.8 Hz, H-3), 3.92 (1H, m, H-1), 3.89 (1H, t, J = 3.2 Hz, H-6), 3.84 (1H, s, O<u>H</u>), 3.81 (3H, s, $CO_2C\underline{H}_3$), 2.38 (1H, m, H-4), 2.03 (1H, ddd, J = 5.2, 3.2, 2.8 Hz, H-7), 1.85 (1H, m, H-8β), 1.60-1.40 (4H, m, H-5, H-8α, 2H-9), 1.41 (3H, s, 3H-13), 1.04 (3H, d, J = 6.8 Hz, 3H-15), 0.99 (3H, s, 3H-14). ^{13}C-NMR δ 178.3 (C-12), 135.0 (C-2), 129.0 (C-3), 77.4 (C-6), 77.2 (C-11), 68.4 (C-1), 53.1 ($CO_2\underline{C}H_3$), 48.6 (C-7), 46.7 (C-5), 36.0 (C-10), 32.8 (C-9), 28.8 (C-4), 24.7 (C-13), 18.2 (C-15), 16.8 (C-8) 15.3 (C-14).

Oxidation of lactone 12 with PCC on alumina.

To a solution of lactone **12** (102 mg, 0.383 mmol) in CH_2Cl_2 (25 mL) was added PCC on basic alumina (926 mg, 1mmol ≅ 806 mg). After 2 h, the mixture was filtered through a short path of basic alumina. Removal of the solvent by rotary evaporation yielded 97 mg (96%) of lactone **14**.

11α-Hydroxy-1-oxo-4αH,5βH,6αH,7αH,10αMe-eudesman-2-en-6,12-olide 14. Colorless crystals. m.p. (EtOAc/hexanes) 133.5-135.4 °C. IR (thin film) ν 3452, 2955, 2893, 1780, 1675, 1464, 1381, 1110, 970. HRMS calcd. for $C_{15}H_{20}O_4$ 264.1362, found 264.1359. ^{1}H-NMR δ 6.64 (1H, dd, J = 10.1, 2.1 Hz, H-3), 5.91 (1H, dd, J = 10.1, 2.8 Hz, H-2), 4.77 (1H, dd, J = 9.2, 7.3 Hz, H-6), 2.70-2.50 (2H, m, H-4, H-7), 1.94 (1H, m, H-9α), 1.80-1.60 (3H, m, 2H-8, H-9β), 1.70 (1H, t, J = 9.2 Hz, H-5), 1.42 (3H, s, 3H-13), 1.35 (3H, d, J = 7.2 Hz, 3H-15), 1.12 (3H, s, 3H-14). ^{13}C-NMR δ 202.9 (C-1), 177.9 (C-12), 154.2 (C-3), 126.0 (C-2), 80.7 (C-6), 74.6 (C-11), 48.0 (C-5), 43.4 (C-10), 43.1 (C-7), 35.0 (C-4), 28.6 (C-9), 21.5 (C-13), 19.9 (C-15), 19.7 (C-8), 18.1 (C-14).

Epoxidation of 14

To a solution of lactone **14** (154 mg, 0,58 mmol) in MeOH (5 mL) was added aq. 35% H_2O_2 (152 μL, 1.470 mmol) and aq. 6N NaOH (0.1 mL, 0.6 mmol). The reaction was stirred at r.t. for 1.5 h, after which time it was neutralized with 1N HCl. The mixture was extracted with EtOAc (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed by rotary evaporation. Purification by flash chromatography (EtOAc/hexane, 2:3) afforded 124 mg (75%) of epoxide **15**.

11α-Hydroxy-2β,3β-epoxy-1-oxo-4αH,5βH,6αH,7αH,10αMe-eudesman-6,12-olide 15. Colorless crystals. m.p. (EtOAc/hexanes) 182.1-184.8 °C. IR (thin film) ν 3433, 2940, 2925, 2870, 1761, 1681, 1454, 1373, 1306, 1201, 1097. HRMS calcd. for $C_{14}H_{20}O_3$ $[M\text{-}CO_2]^+$ 236.1413, found 236.1406. ^{1}H-NMR δ 4.65 (1H, dd, J = 9.2, 7.2 Hz, H-6), 3.38 (1H, dd, J =

3.6, 1.2 Hz, H-3), 3.27 (1H, d, J = 3.6 Hz, H-2), 2.57 (1H, ddd, J = 9.2, 7.2, 5.6 Hz, H-7), 2.25 (1H, ddd, J = 6.8, 6.4, 1.2 Hz, H-4), 1.90-1.80 (1H, m, H-9β), 1.79 (1H, dd, J = 7.2, 6.4 Hz, H-5), 1.78-1.60 (2H, m, H-8, H-9α), 1.54 (1H, m, H-8), 1.44 (3H, d, J = 6.8 Hz, 3H-15), 1.40 (3H, s, 3H-13), 1.06 (3H, s, 3H-14). ^{13}C-NMR δ 206.6 (C-1), 177.6 (C-12), 79.9 (C-6), 74.8 (C-11), 58.7 (C-3), 53.1 (C-2), 44.1 (C-10), 43.5 (C-7), 39.0 (C-5), 32.0 (C-4), 29.2 (C-9), 21.2 (C-13), 20.8 (C-15), 18.1 (C-8), 17.7 (C-14).

Wharton rearrangement of epoxide 15.

To a solution of epoxide **15** (73 mg, 0.26 mmol) in MeOH (10 mL) was added $NH_2NH_2 \cdot H_2O$ (18 μL, 1.3 mmol) and AcOH (0.5 mL) at 0 °C. After 15 min at this temperature, the mixture was heated to reflux for 2 h. Then, H_2O (10 mL) was added. The solution was neutralized with aq. saturated $NaHCO_3$ and the mixture was extracted with EtOAc (3 × 10 mL). Removal of the solvent by rotary evaporation and flash chromatography (EtOAc/hexanes, 2:3) of the crude compound yielded 63 mg (92 %) of **16**.

3β,11α-Dihydroxy-4αH,5βH,6αH,7αH,10αMe-eudesman-1-en-6,12-olide 16. Colorless crystals. m.p. (CH_2Cl_2) 172.4-174.8 °C. IR (thin film) ν 3371, 2960, 2927, 2895, 1758, 1460, 1298, 1210, 1137, 1097, 968. HRMS calcd. for $C_{15}H_{22}O_4$ 266.1518, found 266.1515. ^{1}H-NMR δ 5.69 (1H, dd, J = 9.8, 4.5 Hz, H-2), 5.60, (1H, d, J = 9.8 Hz, H-1), 4.65 (1H, dd, J = 10.4, 7.2 Hz, H-6), 3.92 (1H, t, J = 4.0 Hz, H-3), 2.70 (1H, ddd, J = 7.6, 7.2, 6.4 Hz, H-7), 1.94 (1H, dqd, J = 12.2, 7.2, 4.0 Hz, H-4), 1.79 (1H, td, J = 14.5, 6.9 Hz, H-9β), 1.70-1.45 (3H, m, 2H-8, H-9α), 1.43 (3H, s, 3H-13), 1.19 (3H, d, J = 7.2 Hz, 3H-15), 0.97 (3H, s, 3H-14). ^{13}C-NMR δ 178.5 (C-12), 141.6 (C-1), 124.9 (C-2), 79.4 (C-6), 75.0 (C-11), 66.8 (C-3), 43.3 (C-7), 41.5 (C-5), 35.9 (C-10), 34.6 (C-4), 34.5 (C-9), 21.7 (C-13), 21.2 (C-14), 18.7 (C-8), 15.3 (C-15).

Oxidation of alcohol 16.

To a solution of alcohol **16** (52 mg, 0.20 mmol) in CH_2Cl_2 (25 mL) was added PCC on basic alumina (236 mg, 1mmol ≅ 806 mg). After 2 h, the mixture was filtered through a short path of basic alumina. Removal of the solvent by rotary evaporation yielded 47 mg (91%) of lactone **17**.

11α-Hydroxy-3-oxo-4αH,5βH,6αH,7αH,10αMe-eudesman-1-en-6,12-olide 17. Colorless oil. IR (thin film) ν 3426, 2975, 2932, 2876, 1772, 1718, 1674, 1458, 1380, 1350, 1325, 1304, 1242, 1212, 1182, 1161, 1134, 1098, 968. HRMS calcd. for $C_{15}H_{20}O_4$ 264.1362, found 264.1355. ^{1}H-NMR δ 6.60 (1H, d, J = 9.9 Hz, H-1), 5.86 (1H, d, J = 9.9 Hz, H-2), 4.71 (1H, dd, J = 9.7, 7.2 Hz, H-6), 2.73 (1H, q, J = 7.2 Hz, H-7), 2.55 (1H, dq, J = 12.4, 7.2 Hz, H-4), 1.85 (1H, dd, J = 12.4, 9.7 Hz, H-5), 1.84 (1H, m, H-8α), 1.70-1.60 (3H, m, H-8β, 2H-9), 1.43 (3H, s, 3H-13), 1.32 (3H, d, J = 7.2 Hz, 3H-15), 1.19 (3H, s, 3H-14). ^{13}C-NMR δ 200.4 (C-3), 177.8 (C-12), 157.8 (C-1), 125.8 (C-2), 79.4 (C-6), 74.8 (C-11), 48.0 (C-5), 43.1 (C-4), 43.0 (C-7), 35.6 (C-10), 34.0 (C-9), 21.3 (C-13), 20.7 (C-14), 18.4 (C-8), 13.2 (C-15).

Oxidation of 17.

A mixture of lactone **17** (21 mg, 0.08 mmol) and SeO_2 (27 mg, 0.24 mmol) in dry dioxane (2 mL) was refluxed for 8 h, after which time, the reaction was filtered through celite. The solvent was removed under vacuum. Purification by flash chromatography (EtOAc/hexane, 2:3) yielded 18 mg (86%) of deangeloyldecipienin A, **18**.

11α-Hydroxy-3-oxo-6αH,7αH,10αMe-eudesman-1,2-4,5-dien-6,12-olide 18. Colorless oil. IR (thin film) ν 3445, 2963, 2954, 2935, 2863, 1773, 1655, 1542, 1473, 1419, 1313, 1208, 1042, 986. HRMS calcd. for $C_{15}H_{18}O_4$ 262.1204, found 262.1205. ^{1}H-NMR δ 6.75 (1H, d, J =

10.0 Hz, H-1), 6.23 (1H, d, J = 10.0 Hz, H-2), 5.62 (1H, dq, J = 7.2, 1.6 Hz, H-6), 2.93 (1H, q, J = 7.2 Hz, H-7), 2.41 (1H, s, OH), 2.09 (3H, d, J = 1.6 Hz, 3H-15), 1.98 (1H, m, H-8α), 1.79 (1H, td, J = 13.8, 6.9 Hz, H-9β), 1.75 (1H, m, H-9α), 1.62 (1H, dddd, J = 13.7, 7.2, 6.9, 6.9 Hz, H-8β), 1.34 (3H, s, 3H-13), 1.31 (3H, s, 3H-14).). ^{13}C-NMR δ 185.9 (C-3), 177.3 (C-12), 155.6 (C-1), 151.0 (C-5), 134.8 (C-4), 125.4 (C-2), 76.5 (C-6), 74.8 (C-11), 45.3 (C-7), 39.5 (C-10), 32.8 (C-9), 26.9 (C-14), 20.7 (C-8), 18.3 (C-13), 12.5 (C-15).

Esterification of 18.

To a solution of angelic acid (8.1 mg, 0.081 mmol) in CH_2Cl_2 (1 mL) was added 2,4,6-trichlorobenzoyl chloride (12.5 μL, 0.081 mmol) and Et_3N (11.3 μL, 0.081 mmol). The mixture was stirred for 2 h at r.t. Then, a solution of lactone **18** (9.6 mg, 0.037 mmol) in CH_2Cl_2 (1 mL) was added. The mixture was heated to reflux for 48 h, then diluted with Et_2O (10 mL) and filtered. Solvent was removed under vacuum. Purification by HPLC (EtOAc/hexanes, 1:2) afforded 6 mg of the initial **18**, 3 mg (22 %) of decipienin A, **19**, and 1 mg (8%) of the tiglate ester.

Decipienin A, 19. Colorless oil. IR (thin film) ν 2938, 1791, 1718, 1663. HRMS calcd. for $C_{15}H_{16}O_3$ [M-HOAng]$^+$ 244.1089, found 244.1099. ^{1}H-NMR δ 6.72 (1H, d, J = 9.8 Hz, H-1), 6.25 (1H, d, J = 9.8 Hz, H-2), 6.19 (1H, qq, J = 7.4, 1.4 Hz, H-3′), 5.64 (1H, dq, J = 8.8, 1.7 Hz, H-6), 3.62 (1H, ddd, J = 8.8, 7.3, 6.2 Hz, H-7), 2.12 (3H, d, J = 1.7 Hz, 3H-15), 1.99 (3H, dq, J = 7.4, 1.4 Hz, 3H-4′) 1.95 (1H, m, H-8α), 1.89 (3H, q, J = 1.4 Hz, 3H-5′), 1.73 (1H, m, H-9β), 1.67-1.50 (2H, m, H-8β, H-9α), 1.42 (3H, s, 3H-13), 1.28 (3H, s, 3H-14).). ^{13}C-NMR δ 185.8 (C-3), 173.5 (C-12), 166.3 (C-1'), 155.5 (C-1), 151.6 (C-5), 140.9 (C-3'), 133.6 (C-4), 126.8 (C-2'), 126.0 (C-2), 79.2 (C-11), 76.4 (C-6), 41.9 (C-7), 40.1 (C-10), 34.1 (C-9), 26.4 (C-14), 20.4 (C-8), 19.3 (C-13), 18.7 (C-5'), 16.0 (C-4'), 12.0 (C-15).

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References and Notes

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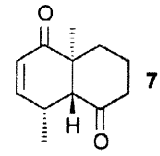
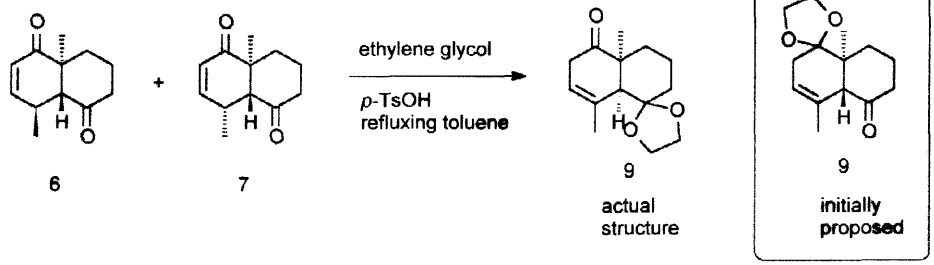


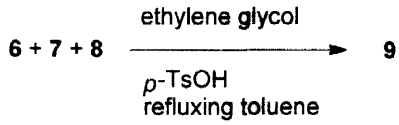
7

When a mixture of **6** and **7** is treated with ethylene glycol, a single product is obtained. In the original paper, a wrong structure is proposed for this compound.



6 **7** **9** **9**

In fact, under these conditions, **8** also gives **9**.



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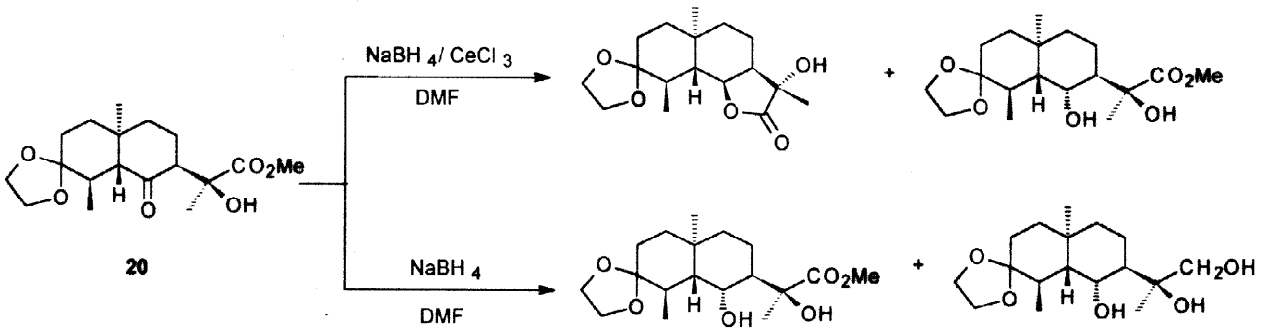
14. We checked these conditions with decalone **20**. The results were different whether or not $CeCl_3$ was used:



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21. The separation of the two epimers can be done more efficiently after reduction of the mixture of the epimers **10a** and **10b** and their subsequent oxidation to afford compound **10b** and the lactone **14**