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SYNTHESIS OF UMBELLIFOLIDE AND THREE NATURAL EUDESMAN-12,8-OLIDES FROM (-)-ARTEMISIN

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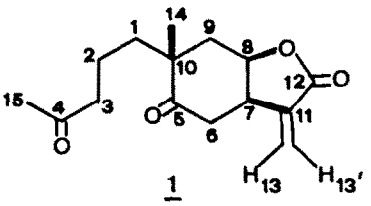
Abstract- The syntheses of the natural 4,5-*seco*eudesmanolide 1 (umbellifolide) and the eudesmanolides 2, 3 and 4 are described. The starting materials are synthetic eudesmane derivatives, the preparation of which from (-)-artemisin had been previously reported.

Umbellifolide 1 is the first 4,5-*seco*eudesmanolide found in nature and was isolated almost simultaneously by Appendino *et al*[1] from *Artemisia umbelliformis* Lam. and by Bohlmann *et al*[2] from *Calea szyszylowczii* Hieron. The same authors could also isolate the hydroperoxyeudesmanolide 2 from the above-mentioned plant species[2,3]. On the other hand, eudesmanolides 3 and 4 were first found by Kaur *et al*[4] in *Inula racemosa* L. and by Wiemer *et al*[5] in *Eupatorium quadrangulare*, respectively. Shortly afterwards, Bohlmann *et al*[6] isolated again 3 and 4 from *Artemisia iwayomogi* Kitam. Interestingly, the enantiomers of 3 and 4 had been reported even earlier in liverworts[7,8]. We have recently published[9,10] the syntheses



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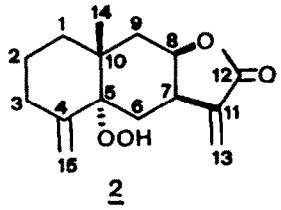

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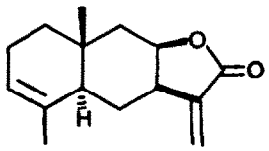

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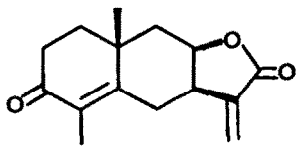

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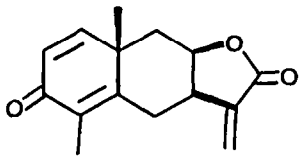
of the natural eudesmanolides 5 (yomogin), 6 (1-deoxyivangustin) and 7 (1-deoxy-8-*epi*ivangustin) using (-)-artemisin 8 as the starting material. Several intermediates described in these papers can also be utilized for the synthesis of compounds 1-4, as we now report. No previous syntheses of these natural products



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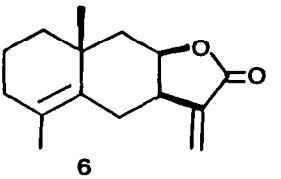

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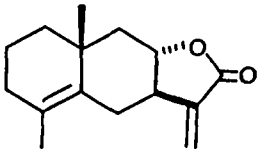

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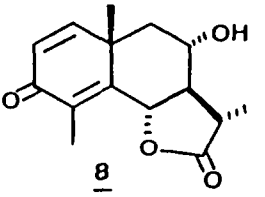

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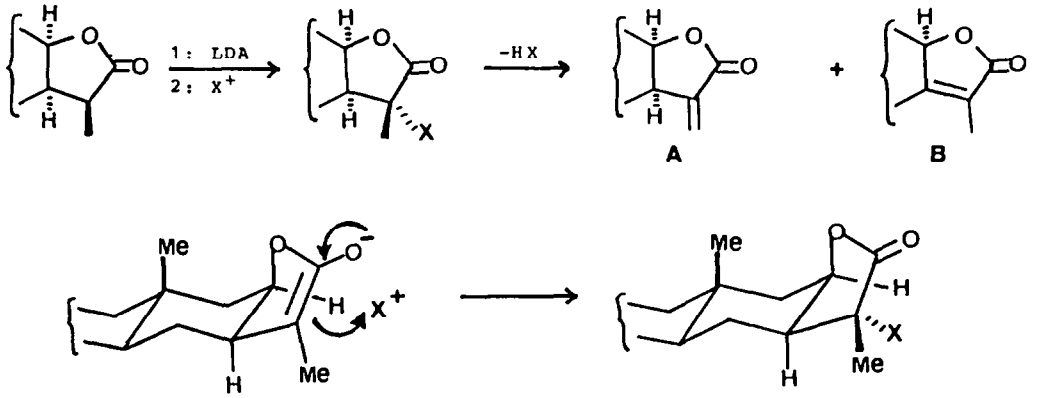
have appeared in the literature.

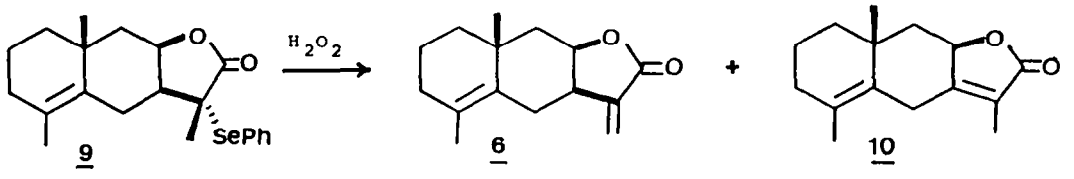
All synthetic targets in our research bear, as evidenced from the structural formulae, an α-methylene-γ-lactone ring *cis* condensed to a decalin or cyclohexane ring. The key problem for the creation of such α-methylene-γ-lactones from the corresponding α-methyllactones is the introduction in the latter of an appropriate leaving group X (Scheme 1). Because of the convex shape of the molecule, electrophilic reagents tend to attack the lactone enolate from the less hindered α-face[11]. The outcome of the subsequent elimination step will depend on whether



Scheme 1

this elimination proceeds by a *syn* (X=ArSe) or by an *anti* pathway (X=Hal). A *syn* pathway should give rise to a mixture of exocyclic (A) and endocyclic (B) double-bond isomers, while an *anti* pathway can be expected to yield only the exocyclic isomer[11].

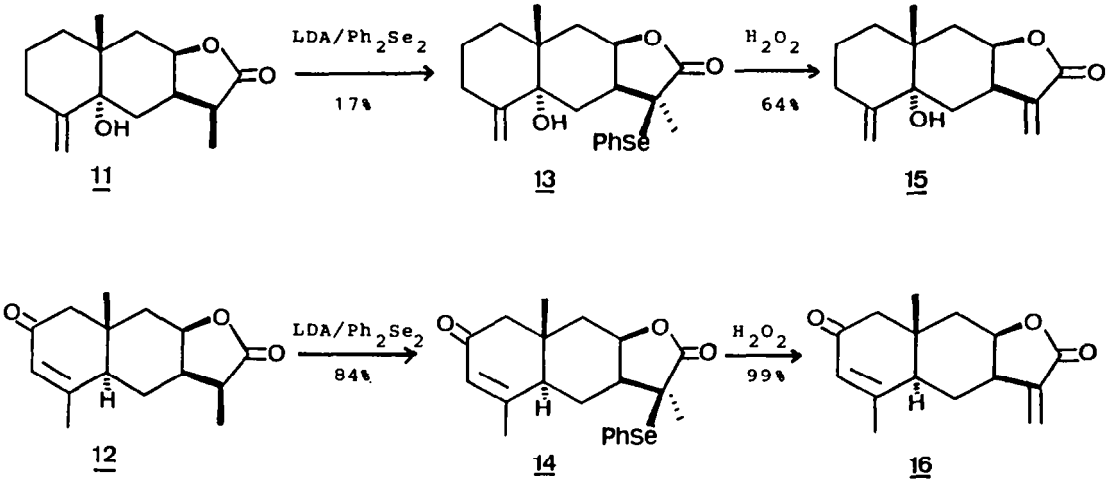
In fact, in our synthesis[9,10] of 1-deoxyivangustin 6 the oxidative elimination in 9 took place with the preferential formation of the endocyclic isomer 10 (61%), the desired 6 being obtained in a rather low yield (13%) (Scheme 2). An



9 6 10

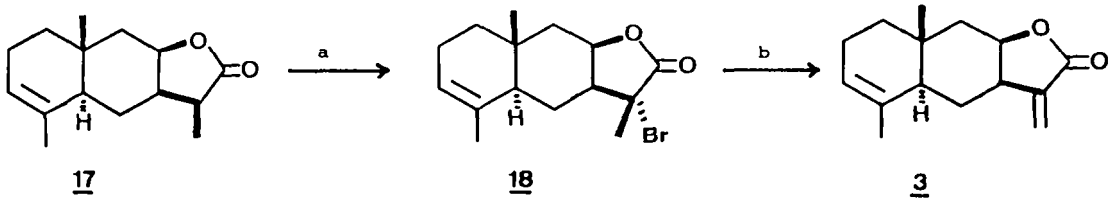
Scheme 2

analogous result had been observed by Yamakawa *et al*[12] in their synthesis of yomogin 5. The same authors, however, reported the selenylation of lactones 11 and 12 taking place from the more hindered β-face (Scheme 3) and founded their opinion on the exclusive formation of the exocyclic double-bond isomers 15 (telekin) and 16 (pinnatifidin) after oxidative elimination[13].



Scheme 3

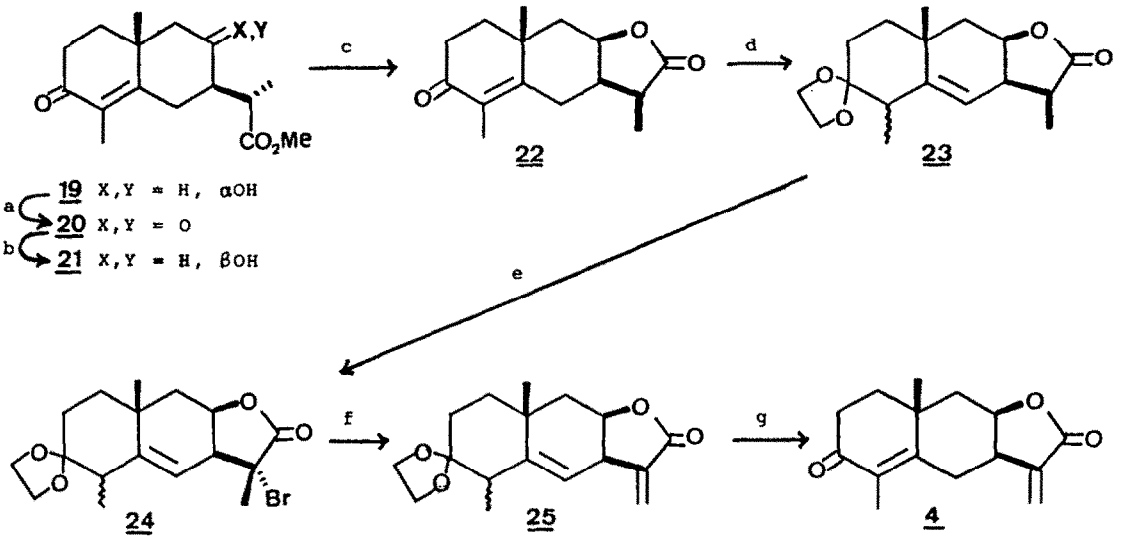
Since this rather unusual stereoselectivity cannot always be reckoned with, we chose to use α-halogenated lactones as the precursors to the desired α-methylenelactones because the former can be expected to undergo exclusively *trans*-elimination[11], affording exocyclic double-bond isomers. In this connection, we examined the α-halogenation of lactone 17[10] as a viable way toward the natural eudesmanolide 3 (Scheme 4). Of several reported halogenation procedures[11,14,15] only the treatment of the enolate of 17 with carbon tetrabromide[15] did allow the preparation of an α-halogenated derivative 18 in a good yield (84%). The configuration at C-11 in compound 18 was deduced from the marked downfield shift (ca. 0.5 ppm) experienced



Scheme 4. a) LDA, -78°, CBr_4. b) DBU, Tol, Δ.

by the NMR signal of H-8 after introduction of the bromine atom, thus pointing to a spatial proximity between both atoms. As expected, basic treatment of 18 with DBU in refluxing toluene yielded 3, uncontaminated with the endocyclic double-bond isomer, in a 46% overall yield from 17.

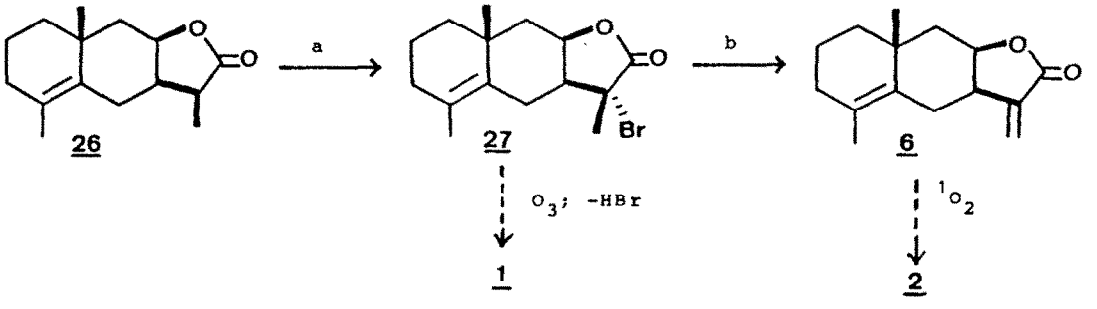
The use of this same sequence for the synthesis of 4 turned out to be less efficient. Compound 22[10] (Scheme 5) could be expected to show competitive nucleo-



Scheme 5. a) $CrO_3 \cdot py_2$, CH_2Cl_2. b) $LiAlH(OtBu)_3$, THF. c) cat. H^+, Δ, C_6H_6. d) (CH_2OH) cat. H^+, C_6H_6, Δ. e) LDA, CBr_4. f) DBU, Tol, Δ. g) aq HCl, THF, Δ.

philic reactivity in its ketone and lactone enolates. Indeed, selenylation of 22 (LDA, Ph_2Se_2) took place at both C-2 and C-11, thus not allowing the preparation of 4 via the same procedure as yomogin[12]. For this reason, we decided to protect the ketone carbonyl group of 22 as its ethyleneketal. As in similar cases[16], formation of the ketal group occurred with double bond migration (22⟶23, Scheme 5). Bromination of 23 under similar conditions as above gave 24 (unknown configuration at C-4), which was sequentially dehydrobrominated and deketalized, affording 4. Unfortunately, the yield in the dehydrobromination step was low (44%), the formation of 25 being accompanied by partial double bond migration toward the endocyclic position and other side reactions. The overall yield in 4 from 22 was thus ca.13%.

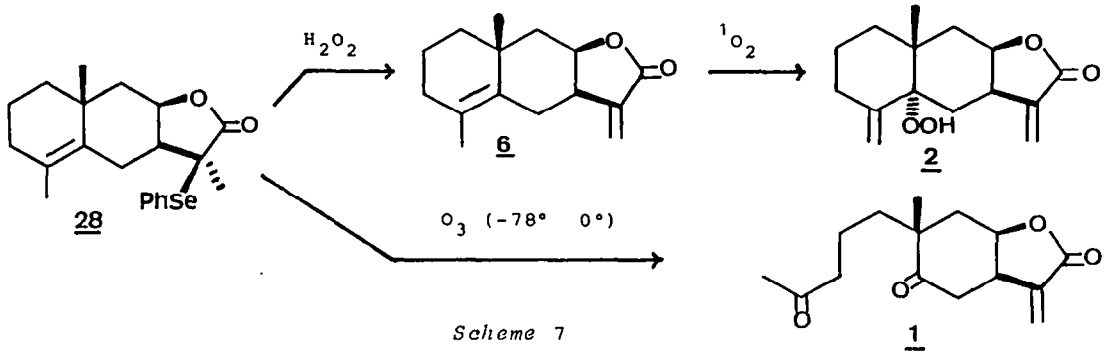
For the syntheses of umbellifolide 1 and the hydroperoxide 2 we planned to start, for the sake of efficiency, from a common intermediate like 27 (Scheme 6). Basic treatment of this product should yield 6 by elimination of HBr, the latter compound being a potential precursor to 2 via sensitized photo-oxigenation[1,17,18]. On the other hand, ozonolytic cleavage of the double bond in 27, followed by HBr elimination should give rise to 1.



Scheme 6. a) LDA, CBr_4. b) DBU, Tol, Δ.

Although we had reported a failure in our attempts[9] to brominate 26, we reexamined this reaction more carefully. In fact, we were now able to obtain 27 from 26[10] by the LDA/CBr_4 procedure. Unfortunately, the yield was unsatisfactory (35%) and could not be improved by variation in the reaction conditions. Furthermore, the dehydrobromination step took place with extensive decomposition of the starting product, the yield in 6 being disappointingly low (less than 10%).

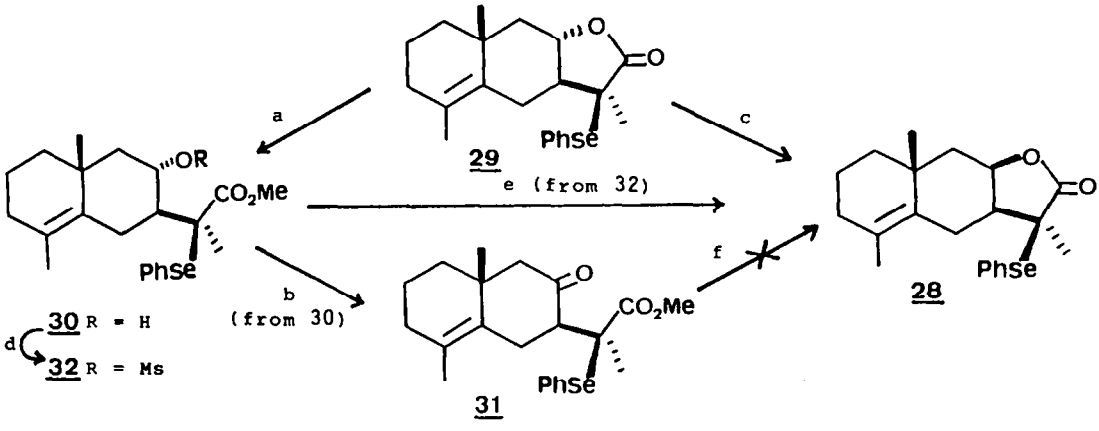
It then occurred to us, as an alternative, that compound 28 would also be a good precursor to both 1 and 2 (Scheme 7) under mild reaction conditions. The β-oriented phenylselenenyl group should undergo oxidative *syn* elimination only in the desired sense, giving the exocyclic α-methylene derivatives. Selective oxidation at the selenium atom ($NaIO_4$ or H_2O_2) and concomitant elimination would afford 6, while low-temperature ozonolysis would simultaneously oxidize the selenium atom



Scheme 7

and cleave the double bond. Since 28, however, is not the product obtained by selenylation of 26, we attempted its synthesis by inversion of the configuration at C-8 in the already described[10] 29 (Scheme 8).

Lactone 29 was saponified and treated *in situ* with ethereal CH_2N_2 to give the hydroxyester 30. After inversion at C-8 by Mitsunobu's procedure[19] failed (recovery of unreacted starting product), we tried the oxidation-reduction[10] method. For instance, Collins reagent ($CrO_3.py_2$) produced decomposition of 30 whereas NCS/SMe_2[20] or DDQ in refluxing dioxane[21] did not give any reaction. Eventually, oxidation of 30 could be performed with Swern's reagent[22] DMSO/TFAA at -65°(Scheme 8).

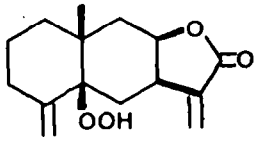


Scheme 8. a) NaOH, EtOH, Δ; aq AcOH, 0°; excess CH_2N_2. b) DMSO, TFAA, -65° 0°, Et_3N. c) NaOH, EtOH, Δ; MsCl; aq NaOH, Δ. d) MsCl, dimethylaminopyridine. e) NaOH, EtOH, Δ. f) $LiAlH(OtBu)_3$, THF, 0°.

However, hydride reduction of 31 took place with decomposition of the starting product: chromatographic inspection of the crude reaction product revealed the presence of yellow selenium-containing by-products, which were not further investigated. The possibility of inversion at C-8 by *intramolecular* nucleophilic attack of the lactone oxygen was then taken into consideration. The hydroxyester 30 was mesylated and the mesylate 32 was treated with hot ethanolic NaOH. Lactone 28 was indeed obtained (Scheme 8) in an overall yield of 30% from 29. We then took notice of a recent paper[23] which described a method for lactone inversion via saponification and sequential treatment of the isolated *dry* sodium salt with mesyl chloride in THF and aqueous NaOH at 50°. In the case of 29, this procedure gave 28 in an overall yield of 52%, based on consumed 29 . According to expectation, 28 could be oxidized selectively at the selenium atom with hydrogen peroxide, affording exclusively 6 in 81% yield. On the other hand, ozonolysis of 28 at -78°, followed by elevation of the temperature to 0°, further stirring for 1 h. and addition of SMe_2 gave 1 in 67% yield (Scheme 7).

A comment about the NMR spectral properties of the epimeric α-selenylated lactones 9 and 28 seems pertinent. The phenylselenenyl group can be expected to exert a deshielding influence on the chemical shifts only in the case of spatially proximate protons. For instance, the NMR signal of H-8 in 28 has practically the same chemical shift as that in 26 (δ ca. 4.5), whereas the absorption of the same proton in 9 lies at markedly lower field (δ 5.01). This can be explained by the spatial proximity of H-8 and the PhSe group in 9 . The same reasoning explains the low-field shift of the NMR signal of H-8 in lactones 18, 24 and 27 , where this hydrogen experiences the deshielding effect of the bromine atom. Since the chemical shift values of H-8 in Yamakawa's compounds 13 (δ 5.12) and 14 (δ 5.05) (Scheme 4) are very similar to that in 9 but not to that in 28 , we would conclude that the assigned configuration[13] of C-11 in 13 and 14 is erroneous and should thus be inverted. However, the reasons for the reported regioselective oxidative elimination in 13 and 14 , to give only 15 and 16 , are not easy to explain.

The hydroperoxide 2 was found, along with its 5β-epimer 33 , in the same plant source as umbellifolide 1 and may thus be a biogenetic precursor to the latter[1,2,3] . We found that lactone 6 could be photo-oxidized to 2 (Scheme 7) under analogous conditions to those reported for related compounds[17,18]. We could not detect, however, the formation of the epimer 33 , although a closely related lactone had been reported[24] to give both epimeric hydroperoxides by photo-oxygenation.



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EXPERIMENTAL

Mps were determined in open capillary tubes and are not corrected. IR spectra were measured as KBr pellets or liquid films on a Perkin Elmer 281 spectrophotometer. UV spectra were registered in EtOH solution. ^{1}H and ^{13}C NMR spectra were measured, respectively, at 200.13 and 50.32 MHz (Bruker AC-200 model) in $CDCl_3$ solution (room temperature), unless otherwise stated. Mass spectra were run by electron impact (70 eV) on a Varian MAT-311A spectrometer. Optical rotations

were measured in $CHCl_3$ solution at a concentration of about 0.2 gr/100 mL. In all experimental procedures, the *usual treatment* means washing the organic layer with brine, drying the solution over anhydrous Na_2SO_4, filtering and concentrating *in vacuo*. The obtained residue is then submitted to column chromatography on silica gel with the indicated solvent mixture as the eluent. The following abreviations are used: THF (tetrahydrofurane); HMPT (hexamethylphosphoric triamide); CSA (camphorsulfonic acid); TMEDA (tetramethylethylenediamine); LDA (lithium diisopropylamide); DBU (1,5-diazabicyclo[5.4.0]undec-5-ene); TFAA (trifluoroacetic anhydride); DMSO (dimethylsulfoxide).

11α-Bromo-5,7,8αH-eudesm-3-en-12,8-olide (18). A solution of *n*BuLi (0.19 mL of a 1.6M solution in hexane, ca. 0.3 mMol) was added at room temperature under Ar via syringe to a solution of diisopropylamine (0.05 mL, ca. 0.35 mMol) in dry THF (1 mL). After stirring for 10 min., the mixture was cooled to -78° in a dry ice-acetone bath. Lactone 17 (40 mg, 0.17 mMol) was dissolved in dry THF (1.5 mL) and added dropwise to the cooled LDA solution. After stirring for 1 h. at -78°, a solution of CBr_4 (100 mg, ca. 0.3 mMol) and HMPT (0.05 mL) in dry THF (1 mL) was added dropwise via syringe. The reaction mixture was stirred for 40 min. at -78°, then for a further 40 min. at -40° and quenched at this temperature with aqueous NH_4Cl (4 mL). The reaction mixture was then extracted with EtOAc (3 x 10 mL) and the organic layer was treated as usually (elution with hexane-EtOAc 9:1). This yielded 18 (34 mg, 64%) as needles, mp 158-159° (from hexane-EtOAc), $[\alpha]_D^{25}$ -41.5°; IR ν_{max} (KBr): 1773 (γ-lactone) cm^{-1}. MS, m/z (% rel.int.): 314/312 (M^+, isotopic pair, 15), 299/297 (M^+-CH_3, 37), 233 (M^+-Br, 13), 232 (M^+-HBr, 10), 217 (M^+-HBr-CH_3, 24), 189 (11), 145 (70), 41 (100). ^1H NMR: δ 5.39 (*m*, 1H; H-3), 4.97 (*m*, 1H; H-8), 2.64 (*ddd*, Js= 12.5, 6.3 and 3.9 Hz; H-7), 2.21 (*dd*, Js= 15.5 and 1.8 Hz; H-9β), 2.10-1.80 (*m*, 4H; H-2α,β,5,6α), 1.93 (*s*, 3H; H-13), 1.63 (br *s*, 3H; H-15), 1.60-1.30 (*m*, 2H; H-1α,β), 1.46 (*dd*, Js= 15.5 and 4.5 Hz; H-9α), 0.98 (*td*, Js= 13.5 and 12.5 Hz; H-6β), 0.85 (*s*, 3H; H-14).

Further elution with the same solvent mixture gave 10 mg unreacted 17. The yield in 18 thus amounts to 84%, based on consumed 17.

5,7,8αH-Eudesma-3,11-dien-12,8-olide (3). Lactone 18 (25 mg, ca. 0.08 mMol) and DBU (0.06 mL, 0.4 mMol) were dissolved in dry toluene (4 mL) and refluxed under Ar for 2 h. The reaction mixture was then poured into 5% aqueous HCl (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was then treated as usually (elution with hexane-EtOAc 9:1). This yielded 3 (10 mg, 55%) as an oil, $[\alpha]_D^{25}$ +93°; IR ν_{max} (film): 1780 (γ-lactone), 1675, 1267 cm^{-1}. MS, m/z (% rel.int.): 232 (M^+, 90), 217 (M^+-CH_3, 100), 171 (82), 145 (68). ^1H NMR (*400 MHz*): δ 6.13 (*d*, J= 1.2 Hz; H-13'), 5.58 (*d*, J= 1.2 Hz; H-13), 5.37 (*m*, 1H; H-3), 4.52 (*td*, Js= 5.1 and 1.5 Hz; H-8), 3.00 (*dddd*, Js= 12.5, 6.5, 5.1 and 1.2 Hz; H-7), 2.15 (*dd*, Js= 15.5 and 1.5 Hz; H-9β), 2.10-1.90 (*m*, 4H; H-2α,β,5,6α), 1.61 (*d*, 3H, J= 0.8 Hz; H-15), 1.45-1.25 (*m*, 3H; H-1α,β,9α), 1.23 (*q*, J≈13 Hz; H-6β), 0.88 (*s*, 3H; H-14).

Methyl (11S)-3,8-Dioxo-7αH-eudesm-4-en-12-oate (20). CrO_3 (100 mg, ca. 1 mMol) was slowly added at 0° portionwise under Ar to a mixture of dry pyridine (2 mL) and dry CH_2Cl_2 (15 mL). After stirring this mixture for 10 min., a solution of hydroxyester 19[9] (140 mg, 0.5 mMol) in dry CH_2Cl_2 (5 mL) was added. Stirring was maintained for 9 h. at 0°, after which the reaction mixture was filtered, washed successively with 0.1N HCl and 5% aqueous $NaHCO_3$ and treated as usually (elution with hexane-EtOAc 3:2). This gave 20[12] (125 mg, 90%) as an oil, $[\alpha]_D^{25}$ +66°. IR ν_{max} (film) 1740 (ester), 1722 (ketone), 1669, 1615 cm^{-1}. UV λ_{max} (ε_{max}): 246 nm (18000). MS, m/z (% rel.int.): 278 (M^+, 24), 263 (M^+-CH_3, 9), 247 (M^+-OCH_3, 14), 246 (M^+-CH_3OH, 20), 218 (20), 202 (16), 191 (100). ^1H NMR: δ 3.70 (*s*, 3H; COOMe), 3.04 (*m*, 1H; H-6α), 2.95 (*m*, 1H; H-11), 2.75-2.55 (*m*, 2H; H-6β,7), 2.55-2.45 (*m*, 2H; H-2α,β) 2.46 (*d*, J= 13.6 Hz; H-9β), 2.38 (*d*, J= 13.6 Hz; H-9α), 2.00-1.80 (*m*, 2H; H-1α,β), 1.85 (*d*, 3H, J= 1.1 Hz; H-15), 1.27 (*d*, 3H, J= 7.2 Hz; H-13), 1.25 (*s*, 3H; H-14).

Methyl (11S)-3-Oxo-8β-hydroxy-7αH-eudesm-4-en-12-oate (21). Diketoester 20 (100 mg, ca. 0.36 mMol) was dissolved in dry THF (8 mL) and treated at 0° with $LiAlH(OBu^t)_3$ (290 mg, ca. 1.14 mMol). After stirring for 6 h. under Ar at this temperature, the reaction was carefully quenched by addition of aqueous NH_4Cl (15 mL). The mixture was then extracted with CH_2Cl_2 (3 x 15 mL) and the organic layer was treated as usually (elution with hexane-EtOAc 3:2). This yielded 21[12] (77.5 mg, 77%) as needles, mp 125-130° (product lactonizes by heating), $[\alpha]_D^{25}$ +64°; IR ν_{max} (KBr): 3600-3300 (OH), 1736 (ester), 1662, 1608 cm^{-1}. UV λ_{max} (ε_{max}): 251 nm (13000). MS, m/z (% rel.int.): 280 (M^+, 33), 262 (M^+-H_2O, 55), 248 (M^+-CH_3OH, 31), 203 (51), 202 (69), 187 (35), 177 (21), 175 (100). ^1H NMR: δ 4.18 (apparent *q*, average J ≈ 2.9 Hz; H-8), 3.72 (*s*, 3H; COOMe), 2.80-2.20 (*m*, 5H; H-2α,β,6α,β,11), 1.93 (*dd*, Js = 14.5 and 2.6 Hz; H-9β), 1.75 (br *s*, 3H; H-15), 1.55 (*dd*, Js= 14.5 and 3.3 Hz; H-9α), 1.41 (*s*, 3H; H-14), 1.23 (*d*, 3H, J= 7 Hz; H-13).

3-Oxo-7,8,11αH-eudesm-4-en-12,8-olide (22). A solution of hydroxyester 21 (70 mg, 0.25 mMol) and CSA (5 mg) in dry benzene (5 mL) was heated at reflux for 90 min. After evaporation of the solvent *in vacuo*, the oily residue was directly

chromatographed on silica gel (elution with hexane-EtOAc 7:3). This yielded 22 (60.5 mg, 98%) with the expected physical properties[10]. The overall yield in 22 fro artemisin 8 amounts to 40%, which compares favorably with that of the described[10] route (ca. 29%).

3,3-Ethylenedioxy-4ξ,7,8,11αH-eudesm-5-en-12,8-olide (23). A solution of lactc ne 22 (53 mg, 0.21 mMol), ethylene glycol (507 mg, 8.2 mMol) and CSA (5 mg) in dry benzene (5 mL) was refluxed for 20 h. A Dean-Stark trap was utilized for the elimination of the water produced in the reaction. The reaction mixture was cooled tc room temperature and poured into brine (10 mL). After extraction with EtOAc (3 x 10 mL), the organic layer was treated as usually (elution with hexane-EtOAc 3:2). This gave 23 (43.5 mg, 70%) as needles, mp 158-159° (from hexane-CH_2Cl_2). IR ν_{max} (KBr): 1762 (γ-lactone), 1175, 1070 cm^{-1}. MS, m/z (% rel.int.): 292 (M^+,1), 248 ($M^+-C_2H_4O$, 2), 206 (1), 99 (100). ^1H NMR: δ 5.23 (br *t*, J≈2.5 Hz; H-6), 4.69 (*ddd*, Js= 5.5, 3.4 and 1 Hz; H-8), 4.10-3.90 (*m*, 4H; ethylene ketal), 3.05 (*ddt*, Js= 8.3 5.5 and 2.5 Hz; H-7), 2.89 (*dq*, Js= 8.3 and 7.1 Hz; H-11), 2.64 (*qt*, Js= 6.6 and 2.5 Hz; H-4), 2.27 (*dd*, Js= 15 and 3.4 Hz; H-9β), 1.60 (*dd*, Js=15 and 1 Hz; H-9α), 1.24 (*d*, 3H, J= 7.1 Hz; H-13), 1.23 (*s*, 3H; H-14), 1.02 (*d*, 3H, J= 6.6 Hz; H-15).

Further elution with the same solvent mixture gave 12 mg unreacted 22, so that the yield in 23 amounts to 90%, based on consumed 22.

3,3-Ethylenedioxy-11α-bromo-4ξ,7,8αH-eudesm-5-en-12,8-olide (24). A solution of *n*BuLi (0.16 mL of a 1.6M solution in hexane, 0.26 mMol) was added at room temperature under Ar via syringe to a solution of diisopropylamine (0.04 mL, 0.28 mMol in dry THF (1 mL). After stirring for 10 min., the mixture was cooled to -78° in a dry ice-acetone bath. Ethylene ketal 23 (38 mg, 0.13 mMol) was dissolved in dry TH (1 mL) and added dropwise to the cooled LDA solution. After stirring for 1 h. at -78°, a solution of CBr_4 (86.5 mg, 0.26 mMol) and HMPT (0.05 mL) in dry THF (1 mL) was added dropwise via syringe. The reaction mixture was stirred for 40 min. at -78°, then for a further 40 min. at -40° and quenched at this temperature with aq. NH_4Cl (4 mL). The reaction mixture was worked up as above (17⟶18). Hexane-EtOAc 3:2 eluted 24 (31 mg, 64%) as needles, mp 140-143° (from hexane-CH_2Cl_2). IR ν_{max} (KBr): 1784 (γ-lactone), 1668, 1180 cm^{-1}. MS, m/z (% rel.int.): 372/370 (M^+, isotopic pair, 0.2), 328/326 ($M^+-C_2H_4O$, 1), 291 (M^+-Br, 0.5), 286/284 (1.5), 99 (100) ^1H NMR: δ 5.21 (br *t*, J≈2.6 Hz; H-6), 5.06 (*ddd*, Js= 5.2, 3.5 and 1.1 Hz; H-8), 4.10-3.90 (*m*, 4H; ethylene ketal), 3.27 (*dt*, Js= 5.2 and 2.6 Hz; H-7), 2.59 (*qt*, Js= 6.6 and 2.6 Hz; H-4), 2.34 (*dd*, Js= 15.2 and 3.5 Hz; H-9β), 1.94 (*s*, 3H; H-13) 1.60 (*dd*, Js= 15.2 and 1.1 Hz; H-9α), 1.22 (*s*, 3H; H-14), 1.00 (*d*, 3H, J= 6.6 Hz; H-15).

3-Oxo-7,8αH-eudesma-4,11-dien-12,8-olide (4). A solution of lactone 24 (26 mg, 0.07 mMol) and DBU (0.05 mL, 0.34 mMol) in dry toluene (3 mL) was heated at reflu under Ar for 1 h. The reaction mixture was then poured into 5% aqueous HCl (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was treated as usually (elution with hexane-EtOAc 3:2). This yielded 25 (9 mg, 44%) as an oil. IR ν_{max} (film): 1,769 (γ-lactone). ^1H NMR: δ 6.20 (*m*, 2H; H-6 and H-13'), 5.63 (*d*, J= 1.6 Hz; H-13), 4.80 (*m*, 1H; H-8), 4.10-3.90 (*m*,4H; ethylene ketal), 2.97 (*qd*, Js= 6.5 and 1.8 Hz; H-4), 2.26 (*dd*, Js= 12.5 and 5.5 Hz; H-9β), 1.51 (*dd*, Js= 12.5 and 6.5 Hz; H-9α), 1.26 (*s*, 3H; H-14), 1.09 (*d*, 3H, J= 6.5 Hz; H-15).

The product obtained in the reaction above was deketalized by treatment with 5% aqueous HCl in refluxing THF (2 mL). After 2 h. reflux, the reaction mixture was cooled, poured into 5% aqueous $NaHCO_3$ and extracted with EtOAc (3 x 5 mL). The organic layer was treated as usually (elution with hexane-EtOAc 1:1). This gave 4 (4 mg, 52%) as needles, mp 160-165° (from hexane-EtOAc), $[\alpha]_D^{25}$ +131°. IR ν_{max} (KBr): 1766 (γ-lactone), 1662 (ketone) cm^{-1}. UV λ_{max} (ε_{max}): 246 (15000). MS, m/z (% rel.int.): 246 (M^+, 100), 231 (M^+-CH_3, 50), 218 (M^+-CO, 21), 204 (39). ^1H NMR : δ 6.36 (*d*, J= 3 Hz; H-13'), 5.71 (*d*, J= 2.6 Hz; H-13), 4.60 (*ddd*, Js= 10.8, 8.3 and 4.8 Hz; H-8), 3.22 (*m*, 1H; H-7), 3.04 (*dd*, Js= 13 and 7.3 Hz; H-6α), 1.82 (*d*, 3H, J= 1 Hz; H-15), 1.26 (*s*, 3H; H-14).

11α-Bromo-7,8αH-eudesm-4-en-12,8-olide (27). A solution of *n*BuLi (0.2 mL of a 1.6M solution in hexane, 0.32 mMol) was added at room temperature under Ar via syringe to a solution of diisopropylamine (0.05 mL, 0.35 mMol) and TMEDA (0.1 mL) in dry THF (2 mL). After stirring for 5 min., the mixture was cooled to -50°. Lactone 26[10] (23.5 mg, 0.1 mMol) dissolved in dry THF (0.5 mL) was added dropwise to the cooled LDA/TMEDA solution. After stirring for 1 h. at -50°, a solution of CBr_4 (116 mg, 0.35 mMol) and HMPT (0.05 mL) in dry THF (1 mL) was added dropwise via syringe. The reaction mixture was stirred for 1 h. at -50° and quenched at this temperature by addition of aqueous NH_4Cl (4 mL). Work-up as above (17⟶18) and column chromatography (elution with hexane-EtOAc 9:1) yielded 27 (11 mg, 35%) as a gum, $[\alpha]_D^{25}$ -53°. IR ν_{max} (film): 1775 (γ-lactone), 1160 cm^{-1}. MS, m/z (% rel.int.): 31 312 (M^+, isotopic pair, 16), 299/297 (M^+-CH_3, 57), 272/270 (2), 257/255 (3), 233 (M^+-Br, 11), 217 ($M^+-HBr-CH_3$, 22), 171 (10), 145 (100), 41 (67). ^1H NMR: δ 4.92 (*m* 1H; H-8), 2.65-2.45 (*m*, 2H; H-6α,7), 2.20 (*dd*, Js= 15.5 and 2 Hz; H-9β), 1.93 (*s*, 3H; H-13), 1.64 (br *s*,3H; H-15), 1.08 (*s*, 3H; H-14).

Dehydrobromination of 27. Bromolactone 27 was dehydrobrominated under the sam reaction conditions as 18. A complex mixture of products was obtained in which th desired 6 was present in less than 10% yield (TLC and NMR examination).

Methyl (11S)-8α-hydroxy-11-phenylseleno-7αH-eudesm-4-en-12-oate (30). A solution of lactone 29[10] (66 mg, 0.17 mMol) in EtOH (4 mL) was treated with 1M aqueous NaOH (0.25 mL) and refluxed under Ar for 1 h. The mixture was then cooled and evaporated to dryness *in vacuo*. The solid residue was treated at 0° with 5% aqueous AcOH (0.5 mL) and then with an excess of ethereal diazomethane. Evaporation of the solvent *in vacuo* and column chromatography on silica gel of the oily residue (elution with hexane-EtOAc 4:1) gave 30 (51 mg, 71%) as a yellowish oil. IR ν_{max} (film): 3600-3300 (OH), 1722 (ester), 741, 693 (aromatic ring) cm^{-1}. ^1H NMR: δ 7.70-7.30 (*m*, 5H; aromatic ring), 4.11 (*ddd*, Js= 11.1, 10 and 4.3 Hz; H-8), 3.52 (*s*, 3H; COOMe), 2.34 (*dd*, Js= 10.5 and 3 Hz; H-6α), 2.19 (*ddd*, Js= 14, 10 and 3 Hz; H-7), 1.90 (*dd*, Js= 12.4 and 4.3 Hz; H-9β), 1.68 (*s*, 3H; H-15), 1.50 (*s*, 3H; H-13), 1.33 (*dd*, Js= 12.4 and 11.1 Hz; H-9α), 1.05 (*s*, 3H; H-14).

Methyl (11S)-8-oxo-11-phenylseleno-7αH-eudesm-4-en-12-oate (31). DMSO (10 µL, 0.17 mMol) was dissolved under Ar in dry CH_2Cl_2 (0.5 mL), cooled to -65° and treated with TFAA (17 µL, 0.12 mMol) at this temperature. After stirring for 40 min., a solution of hydroxyester 30 (21 mg, 0.05 mMol) in dry CH_2Cl_2 (0.25 mL) was added via syringe. The reaction mixture was stirred for 1 h. at -65° and then for a further 30 min. without the cooling bath. Dry triethylamine (30 µL) was added and the stir was continued for 30 min. at room temperature. The mixture was then poured into water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was treated as usually (elution with hexane-EtOAc 9:1). This yielded unreacted 30 (6 mg) and ketone 31 (10 mg, 67% based on consumed 30) as a yellowish oil. IR ν_{max} (film): 1720 (ester), 1710 (ketone), 740, 690 (aromatic ring) cm^{-1}. ^1H NMR: δ 7.65-7.25 (*m*, 5H; aromatic ring), 3.48 (*s*, 3H; COOMe), 3.15-3.00 (*m*, 1H; H-7), 2.33 (*d*, J= 13 Hz; H-9β), 2.18 (*d*, J= 13 Hz; H-9α), 1.71 (br *s*, 3H; H-15), 1.62 (*s*, 3H; H-13), 1.04 (*s*, 3H; H-14).

Methyl (11S)-8α-mesyloxy-11-phenylseleno-7αH-eudesm-4-en-12-oate (32). A solution of hydroxyester 30 (29.5 mg, 0.07 mMol) and 4-dimethylaminopyridine (17 mg, 0.14 mMol) in dry CH_2Cl_2 (3 mL) was cooled to 0°, treated with mesyl chloride (11 µL, 0.14 mMol) and stirred for 10 h. at this temperature. The mixture was then evaporated to dryness *in vacuo* and directly chromatographed on silica gel. Elution with hexane-EtOAc 9:1 gave 32 as needles, mp 85-86° (from MeOH). Yield: 31 mg (89%). IR ν_{max} (KBr): 1723 (ester), 740, 691 (arom. ring) cm^{-1}. ^1H NMR: δ 7.70-7.25 (*m*,5H; arom. ring), 5.14 (*td*, Js= 11.5 and 4.4 Hz; H-8), 3.48 (*s*,3H;COOMe), 3.21 (*s*,3H; $MeSO_2$), 2.57 (*td*, Js= 11.5 and 3 Hz;H-7), 2.43 (*dd*, Js= 13.8 and 3 Hz;H-6α), 2.32 (*dd*, Js= 12.4 and 4.4 Hz; H-9β), 2.10-1.80 (*m*,3H; H-3α,β,6β), 1.77 (br *s*,3H;H-15), 1.55 (*s*,3H;H-13), 1.10 (*s*,3H; H-14).

11β-Phenylseleno-7,8αH-eudesm-4-en-12,8-olide (28). A solution of mesylate 32 (30 mg, 0.06 mMol) in EtOH (7 mL) was treated with 1M aqueous NaOH (0.2 mL) and refluxed under Ar for 2.5 h. The mixture was then cooled and evaporated to dryness *in vacuo*. The residue was neutralized with AcOH (4-5 drops), diluted with benzene (5 mL) and refluxed for 90 min. After evaporation of the solvent *in vacuo*, the residue was directly chromatographed on silica gel (elution with hexane-EtOAc 9:1). This gave 28 (11 mg, 47%) as needles, mp 91-92°(from MeOH). IR ν_{max} (KBr): 1764 (γ-lactone), 735, 689 (arom. ring) cm^{-1}. MS, m/z (% rel.int.): 390 (M^+ for most abundant Se isotope, 10), 314 (3), 233 (M^+-PhSe, 50), 171(14), 145 (40), 41 (100). ^1H NMR: δ 7.75-7.30 (*m*,5H;arom. ring), 4.48 (*ddd*, Js= 9, 7 and 4.6 Hz;H-8), 2.78 (*dd*, Js= 12.3 and 6 Hz;H-6α), 2.44 (*ddd*, Js= 12.3, 7 and 6 Hz; H-7), 2.30 (br *t*, J≈12.3 Hz;H-6β), 2.13 (*dd*, Js= 14 and 9 Hz;H-9β), 2.00-1.85 (*m*, 2H; H-3α,β), 1.69 (*dd*, Js= 14 and 4.6 Hz;H-9α), 1.65 (br *s*,3H;H-15), 1.57 (*s*,3H;H-13), 1.70-1.40 (*m*,4H; H-1α, β,2α,β), 1.14 (*s*, 3H; H-14).

One pot conversion of 29 *into* 28. Lactone 29 (140 mg, 0.36 mMol) was dissolved in EtOH (10 mL), treated with 1M aqueous NaOH (0.5 mL) and refluxed under Ar for 90 min. The mixture was then cooled and the solvent was evaporated to dryness *in vacuo*. The residual salt was dried by repeated azeotropic distillation with benzene, suspended in dry THF (8 mL), cooled to 0° and treated at this temperature with Et_3N (0.25 mL, 1.7 mMol) and mesyl chloride (0.1 mL, 1.27 mMol). After stirring for 45 min., 0.25M aqueous NaOH (6 mL) was added and the reaction mixture was heated at 50°for 1 h. After quenching with 5% aqueous HCl (10 mL), extraction with CH_2Cl_2 (3 x 20 mL) and the usual treatment (hexane-EtOAc 9:1) yielded unreacted 29 (32 mg) and 28 (56 mg, 52% based on consumed 29).

Umbellifolide (1). Ozone-enriched oxygen (0.07 mMol O_3/min) was bubbled for 3 min. through a cooled solution (-78°) of lactone 28 (19.5 mg, 0.05 mMol) in dry CH_2Cl_2 (10 mL). Argon was then bubbled at -78° through the reaction mixture to eliminate the excess of ozone and the dry ice-acetone bath was replaced by an ice bath. After stirring at 0°for 1 h., SMe_2 (0.05 mL) was added and the stir was continued for 2 h. at room temperature. The solvent was then eliminated *in vacuo* and the residue was directly chromatographed on silica gel. Elution with hexane-EtOAc 1:1 and 1:3 gave 1 (9 mg, 68%) as needles, mp 109-110° (from hexane-EtOAc), $[\alpha]_D^{25}$ +57°. IR ν_{max} (KBr): 1750 (γ-lactone), 1700 (ketone) cm^{-1}. MS, m/z (% rel.int.): 264 (M^+,2), 207 (6), 180 (60), 162 (6), 84 (46), 43 (100). ^1H NMR (*250 MHz*): δ 6.35 (*d*, J= 2.8 Hz; H-13'), 5.67 (*d*, J= 2.5 Hz; H-13), 5.00 (*td*, Js= 8.7 and 5.7 Hz; H-8), 3.54 (*dddt*, Js= 8.7, 8.4, 6.8 and 2.6 Hz; H-7), 2.72 (*dd*, Js= 15.5 and 6.8 Hz; H-6α), 2.58 (*dd*, Js= 15.5 and 8.4 Hz; H-6β), 2.44 (apparent *td*, Js= 6.3 and 1.7 Hz; H-3α,β), 2.36 (*dd*, Js= 14.5 and 5.7 Hz; H-9β), 2.13 (*s*,3H;CH_3CO), 1.90(*dd*,

Js= 14.5 and 8.7 Hz;H-9α), 1.55-1.35 (*m*,4H;H-1α,β,2α,β), 1.08 (*s*,3H;H-14). ^{13}C NMR (62.89 MHz): δ 212.33 (C-5), 208.02 (C-4), 169.20 (C-12), 137.83 (C-11), 123.75 (C-13), 73.86 (C-8), 45.81 (C-10), 43.07 (C-3), 40.78 (C-6), 38.02 (C-9), 37.23 (C-7), 36.55 (C-1), 30.07 (C-15), 22.90 (C-14), 17.66 (C-2). The signals have been assigned with the aid of 2D heteronuclear shift correlation[25]. The values of the chemical shift of C-8 and C-12 in the reported spectrum[1] are erroneous.

1-Deoxyivangustin 6 *from* 28. Lactone 28 was oxidized under the conditions reported elsewhere[10]. 1-Deoxyivangustin 6 was obtained as the only compound in 81% yield.

5α-Hydroperoxy-7,8αH-eudesma-4(15),11-dien-12,8-olide (2). Lactone 6 (18.5 mg,0.08 mMol) and Methylene Blue (2 mg) were dissolved in absolute EtOH (10 mL) and photooxygenated for 8 h. at 22±2° under the described conditions[18]. After this time, the solvent was eliminated *in vacuo* and the residue was chromatographed on silica gel. Elution with hexane-EtOAc 4:1 gave 2 as an oil (12 mg, 57%), $[\alpha]_D^{25}$ +130°. IR ν_{max} (film): 3600-3300 (OOH), 1755 (γ-lactone) cm^{-1}.MS, m/z (% rel.int.): 231 (M^+-OOH, 10), 95 (80), 55 (100). ^{1}H NMR: δ 6.15 (*d*, J= 1.2 Hz; H-13'), 5.63 (*d*, J= 1 Hz;H-13), 5.11 (br *s*;H-15'), 4.80 (br *s*;H-15), 4.55 (*td*, Js= 5 and 2.5 Hz;H-8), 3.32 (*m*, 1H;H-7), 2.30 (*dd*,Js= 14.5 and 7 Hz;H-6α), 2.00-1.85 (*m*,2H;H-9α,β), 1.01 (*s*, 3H; H-14). ^{13}C NMR: 170.54 (C-12), 146.29 (C-4), 141.89 (C-11), 120.64 (C-13), 113.30 (C-15), 85.88 (C-5), 76.83 (C-8), 37.61 (C-7), 37.29 (C-10), 35.83 (C-1 or C-9), 35.22 (C-9 or C-1), 32.19 (C-3), 27.92 (C-6), 23.04 (C-14), 21.80 (C-2).

All new products gave satisfactory microanalytical data.

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