Synthesis of yomogin, 1-deoxyivangustin, and 1-deoxy-8-epiivangustin

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Received June 25, 1986

JUAN ALBERTO MARCO, MANUEL ARNO, and MIGUEL CARDA. Can. J. Chem. **65**, 630 (1987).

The chemical transformation of (−)-artemisin **1** into the natural sesquiterpene lactones yomogin **2**, 1-deoxyivangustin **3**, and 1-deoxy-8-epiivangustin **4** is described.

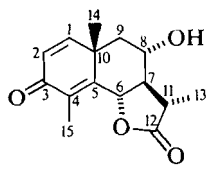
JUAN ALBERTO MARCO, MANUEL ARNO et MIGUEL CARDA. Can. J. Chem. **65**, 630 (1987).

On décrit la transformation chimique du sesquiterpène (−)-artémisine **1** dans les lactones sesquiterpéniques yomogine **2**, déoxy-1 ivangustine **3** et déoxy-1 épi-8 ivangustine **4**.

[Traduit par la revue]

Introduction

α,β-Unsaturated lactones have always aroused very much interest in medicine because of their remarkable biological properties, mainly as cytotoxic, antitumor, and bactericidal agents. Among these compounds, sesquiterpene α-methylene-γ-lactones have been intensively studied (1) from both the medicinal and chemical points of view. Numerous synthetic methods for the α-methylene-γ-lactone grouping have been designed and both total and partial syntheses of this class of compounds have been published (2, 3). Our efforts have focused on the transformation of readily available artemisin **1** into other natural sesquiterpene lactones (4). We now wish to report on our studies concerning the chemical transformation of (−)-artemisin into the natural eudesmanolides yomogin **2**, 1-deoxyivangustin **3**, and 1-deoxy-8-epiivangustin **4**.



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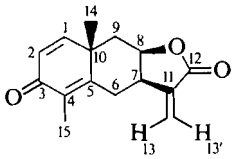

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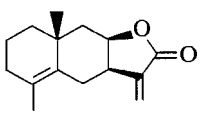

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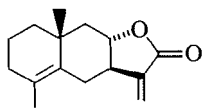

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Yomogin was first isolated by Geissman from *Artemisia princeps* Pamp. (5). The racemic form has been obtained by total synthesis (6), while the natural (−)-form was prepared by Yamakawa *et al.* (7) starting from α-santonin. This last synthesis, however, implied the loss of the stereochemistry of the santonin molecule at C-7, which had to be recreated in a later step, and gave an overall yield of ca. 0.8%. On the other hand, 1-deoxyivangustin and 1-deoxy-8-epiivangustin were isolated for the first time by Bohlmann *et al.* from *Inula helenium* L. and *Artemisia pectinata* Pall., respectively (8, 9). 1-Deoxyivangustin has also been called alloalantolactone (10). Its enantiomeric (−)-form had been isolated even earlier (11) from the liverworts *Diplophyllum albicans* and *D. taxifolium*, and was named diplophyllin.

Apart from the partial conversion of isoalantolactone into **3** by acid isomerization (11), no stereodirected syntheses of **3** or **4** have been published in the literature. Artemisin **1**, which already possesses an oxygen function at C-8 and the appropriate stereochemical configuration at C-7 and C-10, should serve as a very adequate precursor for these and many other eudesman-12,8-olides with either *cis* or *trans* junction between the cyclohexane and lactone rings. According to this expectation, we have synthesized eudesmanolides **2**, **3**, and **4** from (−)-artemisin **1** in, respectively, 7, 10, and 8 steps. Overall yields were 7.5, 2, and 28%, respectively. Since artemisin had already been obtained by total synthesis (12), our syntheses can be formally considered as total syntheses of the above-mentioned compounds.

Results and discussion

A key step for the creation of the 12,8-lactone ring is the reductive cleavage of the C6—O bond in artemisin with subsequent relactonization to C-8. This reaction had already been described for α-santonin (13) and requires epimerization at C-6 prior to reduction with Zn dust. Indeed, artemisin **1** could be easily epimerized at C-6 (4*b*) by a modification of Sumi's method (14), giving **5** in ca. 60% yield. Zn reduction and esterification afforded the 8α-hydroxyester **6**, which could be lactonized almost quantitatively to lactone **7** (12*a*). By hydrogenation in the presence of Wilkinson catalyst, **7** gave **11** (15) in 95% yield. The overall yield of **11** from **1** was thus 33–35% (Scheme 1). Since epimerization at C-6 of 1,2-dihydro-α-santonin takes place with much better yields (16) than that of α-santonin, we also examined this alternative. Lactone **11** was obtained via 1,2-dihydroartemisin **8** in an overall yield of 58–60% from **1**.

Compound **11** was converted into the normal eudesmanolide **4** in a straightforward manner. By reaction with ethanedithiol, **11** gave the thioketal **12**, which yielded, by treatment with active Raney nickel, the unsaturated lactone **13** (17), contaminated with a small percentage (ca. 5%) of a double-bond isomer (16). Phenylselenylation and subsequent oxidation afforded **4** in an overall yield of ca. 49% from **11** (Scheme 2). The compound had physical and spectral properties identical with those reported by Bohlmann *et al.* (9).

For the synthesis of the eudesman-12,8β-olides **2** and **3**, an

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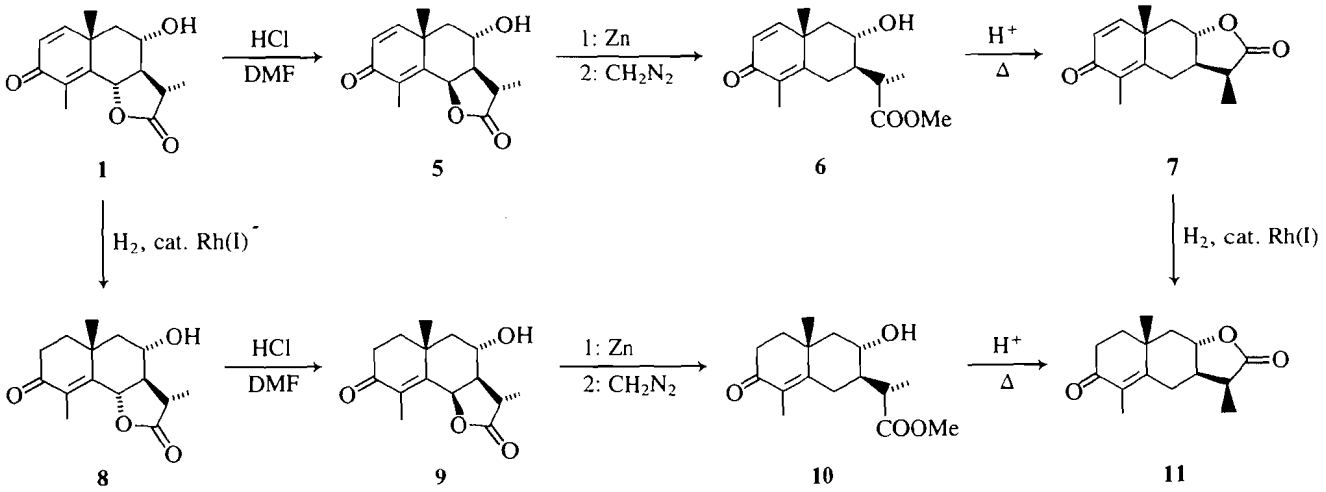
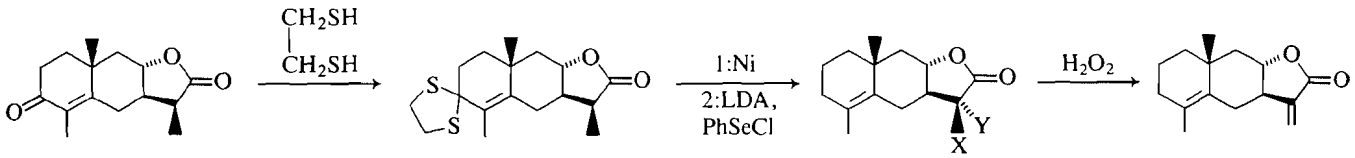
Printed in Canada / Imprimé au Canada



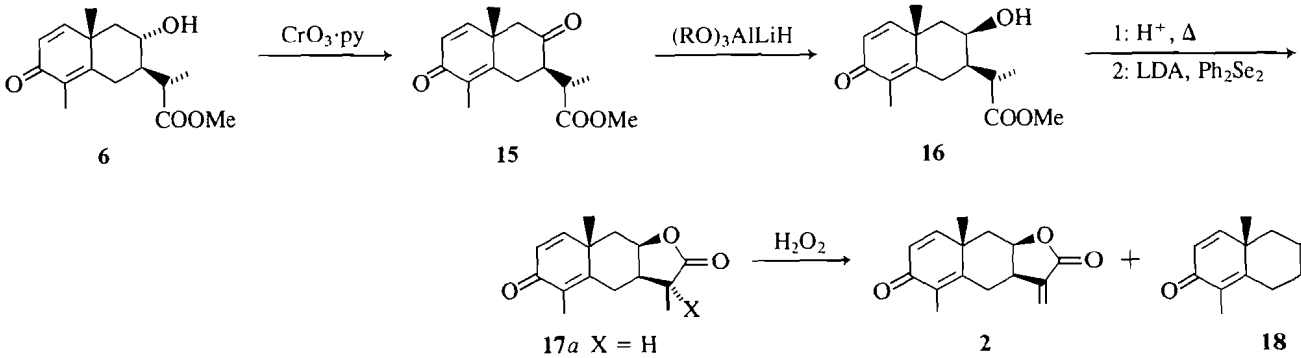
1 5 6 7 8 9 10 11

SCHEME 1



11 12 13 X = Me, Y = H; 14 X = SePh, Y = Me 4

SCHEME 2



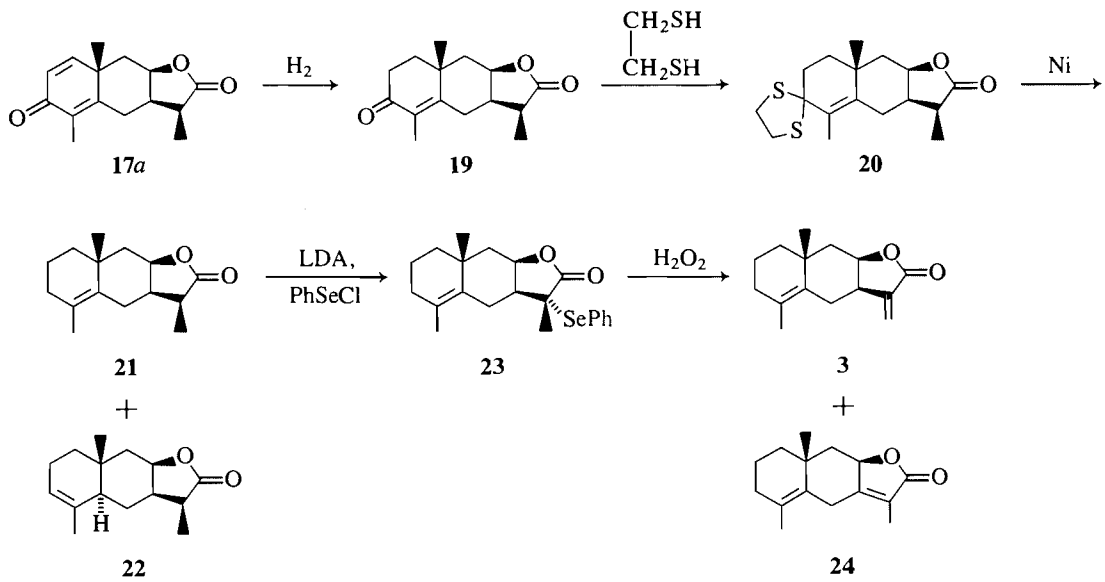
6 15 16 17*a* X = H; 17*b* X = SePh 2 18

SCHEME 3

inversion of the configuration at C-8 is necessary. This was achieved via oxidation–reduction of the hydroxyester **6**. Oxidation with a modified Collins reagent (18) yielded the diketone **15**, which was subsequently reduced with LiAlH $(OBu^t)_3$. The 8β-hydroxyester **16** (80% overall yield from **6**) cyclized quantitatively to the *cis*-lactone **17***a* by brief heating in benzene with catalytic amounts of camphorsulfonic acid. Compound **17***a*, an 11,13-dihydroyomogin, had been already obtained from α-santonin by Yamakawa *et al.* (7*a*) and converted to yomogin **2** and the endocyclic double-bond isomer **18** by the phenylselenylation–oxidation procedure (Scheme 3).

The same sequence of hydrogenation, thioketalization, and desulfurization that had been utilized for the synthesis of lactone **13** proved useful for the preparation of the *cis*-isomer **21** (Scheme 4) in an overall yield of 47% from **17***a*. As in the former case (**12** → **13**), the desulfurization reaction gave not only the desired Δ^4-eudesmanolide **21** (17) but also a certain amount (ca. 13%) of the Δ^3-isomer **22**, which could be separated by chromatography. No other by-products were noted. A secure stereochemical assignment for **22** could be made from a 500-MHz ^{1}H nmr spectrum, in which the signals of H-5, H-6α, and H-6β were resolved. The enantiomers of compounds **21** and **22** have been described in the literature (11, 19).

By selenylation under rather strict conditions (4*b*), **21** gave **23**, in which attack of the selenylating agent proceeded from the less hindered convex α-face. As a consequence, the phenylselenyl group was located in a *syn* relationship to H-7 and the oxidative elimination step took place toward both H-7 and H-13, giving a mixture of two double-bond isomers, as in the case of yomogin (7*a*). The less abundant reaction product was shown to be identical in its spectral properties with 1-deoxy-



SCHEME 4

ivangustin **3** (8). The main reaction product was the unstable endocyclic double-bond isomer **24**.

Experimental

Data have been taken in part from the Ph.D. Thesis of M. Carda. Infrared spectra were recorded as KBr pellets (solids) or as films (oils) on a Perkin Elmer model 281 spectrophotometer. The uv spectra were measured in EtOH solution. Mass spectra were run by electron impact (70 eV) on a Varian MAT-311A spectrometer. The ^{1}H nmr spectra were registered, unless otherwise stated, at 200.13 MHz ($CDCl_3$ solution) on a Bruker AC-200 spectrometer. The signals of the hydrogen atoms were assigned with the aid of decoupling experiments and 2D-nmr spectroscopy (COSY). Melting points were determined on a Büchi melting point apparatus and are not corrected. Optical rotations were measured in $CHCl_3$ solutions (*c* 0.1–0.3 g/100 mL).

THF was distilled under Ar from $LiAlH_4$ and used immediately. DMF was distilled from CaH_2, benzene and CH_2Cl_2 were distilled from anhydrous $CaCl_2$, and all were kept over molecular sieves. MeOH and AcOH (Merck analytical grades) were used as received.

6-Epiartemisin, 5

Artemisin (1.3 g, ca. 5 mmol) was dissolved in 20 mL of dry DMF containing 5% hydrogen chloride. The solution was heated under Ar for 4 h at 90°C, then poured into water (50 mL) and extracted with CH_2Cl_2 (5 × 30 mL). The organic layer was then washed with 5% aqueous $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The oily residue obtained was then chromatographed on silica gel. Elution with hexane–EtOAc 1:4 gave 728 mg (56%) of 6-epiartemisin **5** as white needles, mp 159–160°C (from hexane–CH_2Cl_2) (lit. (14) mp 156–157°C); $[\alpha]_D^{25}$ −191° (lit. (14) $[\alpha]_D^{25}$ −198°), with the expected spectroscopic properties; ^{1}H nmr, δ (ppm): 6.77 (d, *J* = 9.8 Hz, H-1), 6.27 (d, *J* = 9.8 Hz, H-2), 5.62 (d, *J* = 5.5 Hz, H-6), 3.99 (ddd, *J* = 11.7, 9.9, and 4.3 Hz, H-8), 2.99 (q, *J* = 7.7 Hz, H-11), 2.08 (s, 3H, H-15), 2.03 (dd, *J* = 12.5 and 4.3 Hz, H-9β), 2.02 (dd, *J* = 9.9 and 5.5 Hz, H-7), 1.50 (dd, *J* = 12.5 and 11.7 Hz, H-9α), 1.45 (d, 3H, *J* = 7.7 Hz, H-13), 1.32 (s, 3H, H-14).

Further elution enabled the recovery of 81 mg of unreacted artemisin. The yield of **5** thus amounts to ca. 60%, based on consumed **1**.

Methyl (11S)-3-oxo-8α-hydroxy-7αH-eudesma-1,4-dien-12-oate, 6

Activated Zn dust (1.7 g) and anhydrous AcOH (0.3 mL) were added to a solution of lactone **5** (700 mg, 2.67 mmol) in anhydrous MeOH (12 mL). After refluxing under Ar for 15 min, the reaction mixture was cooled to room temperature and directly treated with a great excess of ethereal diazomethane, until persistence of a pale yellow colour. The resulting cloudy solution was then filtered and concentrated *in vacuo*, yielding an oily residue, which was chromatographed on silica gel. Elution with hexane–EtOAc 1:1 gave 475 mg (64%) of a colorless oil, $[\alpha]_D^{25}$ −14°, which was identified as **6** by its spectral properties; ir (film), ν_{max}: 3600–3300 (br s), 1727 (s), 1655 (s) cm^{-1}; uv, λ_{max} (log ε_{max}): 240 nm (4.07); ^{1}H nmr, δ (ppm): 6.73 (d, *J* = 9.8 Hz, H-1), 6.23 (d, *J* = 9.8 Hz, H-2), 4.05 (ddd, *J* = 11, 10.5, and 4.5 Hz, H-8), 3.73 (s, 3H, COOMe), 2.96 (qd, *J* = 7.2 and 2.8 Hz, H-11), 2.82 (dd, *J* = 14.1 and 3.8 Hz, H-6α), 2.19 (ddq, *J* = 14.1, 13.6, and 1.1 Hz, H-6β), 2.10 (dd, *J* = 12.5 and 4.5 Hz, H-9β), 1.92 (d, 3H, *J* = 1.1 Hz, H-15), 1.69 (dddd, *J* = 13.6, 10.5, 3.8, and 2.8 Hz, H-7), 1.30 (d, 3H, *J* = 7.2 Hz, H-13), 1.30 (dd, *J* = 12.5 and 11 Hz, H-9α), 1.24 (s, 3H, H-14); ms *m/z* (% rel. int.): 278 (M^+, 13), 260 (28), 246 (18), 218 (10), 200 (22), 185 (44), 173 (100). *Anal.* calcd. for $C_{16}H_{22}O_4$: C 69.06, H 7.91; found: C 69.29, H 7.77.

3-Oxo-7,11α,8βH-eudesma-1,4-dien-12,8-olide, 7

A solution of hydroxyester **6** (100 mg, 0.36 mmol) and camphorsulfonic acid (CSA) (10 mg) in dry benzene (8 mL) was heated at reflux for 90 min. After evaporation of the solvent *in vacuo*, the oily residue was chromatographed on silica gel. Elution with hexane–EtOAc 1:1 gave 86 mg (97%) of lactone **7** as white needles, mp 108–109°C (from hexane–CH_2Cl_2) (lit. (12*a*) mp 151–154°C); $[\alpha]_D^{25}$ −144°; and the expected ir, uv, and mass spectra; ^{1}H nmr, δ (ppm): 6.77 (d, *J* = 9.8 Hz, H-1), 6.27 (d, *J* = 9.8 Hz, H-2), 4.49 (td, *J* = 11.6 and 4.2 Hz, H-8), 2.99 (dd, *J* = 13.6 and 3.2 Hz, H-6α), 2.79 (quintuplet, *J* = 7.6 Hz, H-11), 2.37 (dd, *J* = 11.6 and 4.2 Hz, H-9β), 2.28 (tq, *J* = 13.6 and 1.1 Hz, H-6β), 1.98 (dddd, *J* = 13.6, 11.6, 7.6, and 3.2 Hz, H-7), 1.94 (d, 3H, *J* = 1.1 Hz, H-15), 1.62 (t, *J* = 11.6 Hz, H-9α), 1.33 (s, 3H, H-14), 1.30 (d, 3H, *J* = 7.6 Hz, H-13).

1,2-Dihydro-6-epiartemisin, 9

1,2-Dihydroartemisin **8** (4*e*) (630 mg, 2.38 mmol) was treated as above (**1** → **5**) by heating for 45 min in 5% HCl/DMF. After work-up, column chromatography (elution with hexane–EtOAc 3:7) yielded 598 mg (95%) of lactone **9** as colorless needles, mp 172–173°C (from ether), $[\alpha]_D^{25}$ −71°; ir (KBr), ν_{max}: 3600–3300 (br s), 1775 (s), 1666 (s) cm^{-1}; uv, λ_{max} (log ε_{max}): 242 nm (3.96); ^{1}H nmr, δ (ppm): 5.54 (d, *J* = 5.6 Hz, H-6), 3.90 (ddd, *J* = 11.8, 9.9, and 3.8 Hz, H-8), 2.98 (q, *J* = 7.7 Hz, H-11), 2.72 (ddd, *J* = 18, 14.1, and 5.9 Hz, H-2β), 2.51 (ddd, *J* = 18, 5.1, and 2.4 Hz, H-2α), 2.00–1.90 (m, 1H, overlapped; H-1α), 2.05 (dd, *J* = 9.9 and 5.6 Hz, H-7), 1.93 (s, 3H, H-15), 1.85 (dd, *J* = 13 and 3.8 Hz, H-9β), 1.80 (ddd, *J* = 13.3, 5.9, and 2.4 Hz, H-1β), 1.45 (dd, *J* = 13 and 11.8 Hz, H-9α), 1.43 (d, 3H, *J* = 7.7 Hz, H-13), 1.28 (s, 3H, H-14); ms *m/z* (% rel. int.): 264

(M^+, 100), 249 (41), 246 (5), 231 (13), 221 (20), 191 (26), 137 (42). *Anal.* calcd. for $C_{15}H_{20}O_4$: C 68.18, H 7.57; found: C 68.25, H 7.68.

Methyl (11S)-3-oxo-8α-hydroxy-7αH-eudesm-4-en-12-oate, ***10***

In a similar procedure as above (**5** → **7**), 600 mg (2.27 mmol) of lactone **9** was allowed to react with activated Zn dust (1.45 g) and acetic acid (0.25 mL) in anhydrous MeOH (10 mL). After refluxing under Ar for 15 min, the reaction mixture was cooled to room temperature, treated with excess of ethereal diazomethane, filtered, concentrated *in vacuo*, and chromatographed on silica gel. Elution with hexane–EtOAc 1:1 gave **10** (410 mg, 65%) as colorless needles, mp 120–121°C (from ether); $[\alpha]_D^{25}$ +58°; ir (KBr), ν_{max}: 3600–3300 (br s), 1735 (s), 1660 (s), 1612 (m) cm^{-1}; uv, λ_{max} (log ε_{max}): 244 nm (3.95); ^1H nmr, δ (ppm): 3.93 (ddd, J = 11.1, 10.5, and 4.2 Hz, H-8), 3.71 (s, 3H, COOMe), 2.90 (qd, J = 7.2 and 2.7 Hz, H-11), 2.71 (dd, J = 14.9 and 3.6 Hz, H-6α), 2.50 (ddd, J = 17.5, 12, and 7 Hz, H-2β), 2.38 (ddd, J = 17.5, 5.3, and 3.5 Hz, H-2α), 2.03 (tq, J = 14.9 and 1.3 Hz, H-6β), 1.93 (dd, J = 12.7 and 4.2 Hz, H-9β), 1.90–1.70 (m, 3H, overlapped; H-1α/β and H-7), 1.77 (d, 3H, J = 1.3 Hz, H-15), 1.37 (dd, J = 12.7 and 11.1 Hz, H-9α), 1.25 (d, 3H, J = 7.2 Hz, H-13), 1.20 (s, 3H, H-14); ms, *m/z* (% rel. int.): 280 (M^+, 49), 262 (84), 248 (15), 247 (34), 234 (18), 219 (7), 215 (7), 202 (100), 187 (48), 175 (83), 159 (33), 147 (76). *Anal.* calcd. for $C_{16}H_{24}O_4$: C 68.57, H 8.57; found: C 68.69, H 8.43.

3-Oxo-7,11α,8βH-eudesm-4-en-12,8-olide, ***11***

(A) By hydrogenation of **7**: Freshly prepared Wilkinson catalyst (15 mg, 16.2 μmol) was suspended in dry benzene (1 mL) and stirred under H_2 atmosphere until complete dissolution (20–30 min). A solution of lactone **7** (70 mg, 0.28 mmol) in dry C_6H_6–EtOH 1:1 (4 mL) was then added via syringe. After stirring for 12 h at room temperature, the hydrogenation mixture was concentrated *in vacuo* and the brownish oily residue was chromatographed on silica gel. Elution with hexane–EtOAc 7:3 gave 67 mg (95%) of compound **11** as white needles, mp 136–137°C (from hexane–CH_2Cl_2) (lit. (15) mp 142°C); $[\alpha]_D^{25}$ +21° (lit. (15) $[\alpha]_D^{18}$ +19.4°), with the expected ir, uv, and mass spectra; ^1H nmr, δ (ppm): 4.44 (ddd, J = 11.9, 10.5, and 4 Hz, H-8), 2.90 (dd, J = 13.7 and 2 Hz, H-6α), 2.76 (quintuplet, J = 7.6 Hz, H-11), 2.58 (ddd, J = 17.5, 13.7, and 5.5 Hz, H-2β), 2.46 (ddd, J = 17.5, 5.2, and 3.1 Hz, H-2α), 2.24 (dd, J = 11.9 and 4 Hz, H-9β), 2.16 (tq, J = 13.7 and 1.2 Hz, H-6β), 2.15–1.80 (m, 3H, H-1α/1β and H-7), 1.80 (d, 3H, J = 1.2 Hz, H-15), 1.62 (t, J = 11.9 Hz, H-9α), 1.31 (s, 3H, H-14), 1.26 (d, 3H, J = 7.6 Hz, H-13).

(B) By lactonization of **10**: By the same procedure as in the transformation **6** → **7**, 56 mg of lactone **10** (0.2 mmol) and CSA (5 mg) were refluxed in dry benzene (4 mL) for 90 min. Column chromatography on silica gel (elution with hexane–EtOAc 7:3) gave 48.5 mg (98%) of compound **11**.

3,3-Ethanedithio-7,11α,8βH-eudesm-4-en-12,8-olide, ***12***

A modification of the published procedure (15) was utilized: Lactone **11** (57 mg, 0.23 mmol), ethanedithiol (0.15 mL, 1.78 mmol), and $BF_3 \cdot OEt_2$ (40 μL) were dissolved in glacial acetic acid (1 mL) and stirred for 9 h at room temperature. The reaction mixture was then poured into water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography on silica gel (elution with hexane–EtOAc 19:1) of the residue yielded **12** (61 mg, 82%) as white needles, mp 170–171°C (from hexane–ether) (lit. (15) mp 158°C); $[\alpha]_D^{25}$ +22° (lit. (15) $[\alpha]_D^{19}$ +43.6°), with the expected ir, uv, and mass spectra; ^1H nmr, δ (ppm): 4.37 (ddd, J = 11.7, 10.7, and 4.1 Hz, H-8), 3.50–3.15 (m, 4H, thioketal hydrogens), 2.80–2.60 (m, 1H, overlapped; H-6α), 2.68 (quintuplet, J = 7.7 Hz, H-11), 2.32 (ddd, J = 14, 12, and 3.4 Hz, H-2β), 2.21 (ddd, J = 14, 4.8, and 3.5 Hz, H-2α), 2.11 (dd, J = 11.7 and 4.1 Hz, H-9β), 1.91 (s, 3H, H-15), 1.85 (ddd, J = 13.5, 12, and 3.5 Hz, H-1α), 1.67 (ddd, J = 13.5, 4.8, and 3.4 Hz, H-1β), 1.47 (t, J = 11.7 Hz, H-9α), 1.21 (d, 3H, J = 7.7 Hz, H-13), 1.15 (s, 3H, H-14).

7,11α,8βH-Eudesm-4-en-12,8-olide, ***13***

Approximately 1 g active W-2 Raney nickel was added at once to a solution of thioketal **12** (50 mg, ca. 0.15 mmol) in MeOH (3 mL). The mixture was stirred for 8 min at room temperature and rapidly quenched by addition of ethanedithiol (0.1 mL). The reaction mixture was then filtered through a pad of silica gel (elution with EtOAc). The organic solution was then concentrated *in vacuo* and chromatographed on silica gel. Elution with hexane–EtOAc 8:2 gave **13** as a colorless oil (30 mg, 83%), homogeneous by tlc, which was shown by nmr to contain a small percentage (ca. 5%) of a double-bond isomer, probably the Δ^3-isomer (16). Elimination of this minor impurity took place in the chromatographic separation after the next step. The compound gave the expected ir and mass spectra; ^1H nmr, δ (ppm): 4.39 (ddd, J = 11.5, 10.5, and 4 Hz, H-8), 2.75–2.60 (m, 2H, H-6α and H-11), 2.06 (dd, J = 11.5 and 4 Hz, H-9β), 2.10–1.80 (m, 4H, H-3α/3β, H-6β, and H-7), 1.61 (br s, 3H, H-15), 1.70–1.40 (m, 4H, H-1α/1β and 2α/2β), 1.39 (t, J = 11.5 Hz, H-9α), 1.19 (d, 3H, J = 7.7 Hz, H-13), 1.08 (s, 3H, H-14).

11β-Phenylseleno-7α,8βH-eudesm-4-en-12,8-olide, ***14***

A solution of *n*BuLi (0.14 mL of a 1.6 *M* solution in hexane, 0.22 mmol) was added at room temperature under Ar via syringe to a solution of diisopropylamine (33 μL, 0.23 mmol) in dry THF (0.2 mL). After stirring for 15 min, the mixture was cooled to −78°C (Dry Ice – acetone bath). Lactone **13** (26 mg, 0.11 mmol) was dissolved in dry THF (0.5 mL) and added dropwise (5 min) to the cooled LDA solution. After stirring for 1 h at −78°C, a solution of Ph_2Se_2 (68 mg, 0.22 mmol) and HMPT (40 μL) in dry THF (0.5 mL) was added dropwise via syringe (5 min). The reaction mixture was stirred for 40 min at −78°C, then for a further 40 min at −40°C, and was quenched at this temperature with 0.5 *N* HCl (0.7 mL). The reaction mixture was then poured into water (5 mL) and extracted with EtOAc (3 × 5 mL), and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* yielded a yellowish oil, which was chromatographed on silica gel. Elution with hexane–EtOAc 19:1 gave **14** (34 mg, 79%) as colorless needles, mp 154–155°C (from MeOH); ir (KBr), ν_{max}: 1770 (s), 1580 (m), 1475 (m), 736 (m), 689 (m) cm^{-1}; ^1H nmr, δ (ppm): 7.70–7.25 (m, 5H, aromatic hydrogens), 4.60 (ddd, J = 11.8, 10.6, and 4.2 Hz, H-8), 2.80 (dd, J = 13.5 and 3.5 Hz, H-6α), 2.07 (dd, J = 11.8 and 4.2 Hz, H-9β), 2.10–1.90 (m, 4H, H-3α/3β, H-6β, and H-7), 1.80–1.40 (m, 4H, H-1α/1β and H-2α/2β), 1.65 (br s, 3H, H-15), 1.54 (s, 3H, H-13), 1.38 (t, J = 11.8 Hz, H-9α), 1.13 (s, 3H, H-14). *Anal.* calcd. for $C_{21}H_{26}O_2Se$: C 64.79, H 6.68, Se 20.30; found: C 64.91, H 6.80, Se 20.10.

1-Deoxy-8-epiivangustin, ***4***

Hydrogen peroxide (90 μL of a 30% aqueous solution, ca. 0.8 mmol) was added at 0°C to a solution of **14** (31 mg, ca. 0.08 mmol) and AcOH (10 μL) in THF (0.5 mL). After stirring for 1 h at 0°C, the reaction mixture was poured into 5% aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 5 mL). The organic layer was washed several times with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and chromatographed on silica gel. Hexane–EtOAc 8:2 eluted a colorless oil (17.5 mg, 94%), $[\alpha]_D^{25}$ −46°, with spectral properties coincident with those reported by Bohlmann *et al.* (9) for 1-deoxy-8-epiivangustin **4**; ir (film), ν_{max}: 1770 (s), 1670 (w), 983 (m) cm^{-1}; ^1H nmr, δ (ppm): 6.09 (d, J = 3.2 Hz, H-13′), 5.44 (d, J = 3 Hz, H-13), 4.11 (ddd, J = 12.1, 10.9, and 3.9 Hz, H-8), 3.00 (dd, J = 13.6 and 3.3 Hz, H-6α), 2.29 (ddq, J = 12.3, 10.9, and 3.1 Hz, H-7), 2.09 (dd, J = 11.5 and 3.9 Hz, H-9β), 2.20–1.80 (m, 3H, H-3α/3β and H-6β), 1.66 (br s, 3H, H-15), 1.70–1.40 (m, 4H, H-1α/1β and H-2α/2β), 1.51 (dd, J = 12.1 and 11.5 Hz, H-9α), 1.10 (s, 3H, H-14); ms, *m/z* (% rel. int.): 232 (M^+, 33), 217 (100), 204 (3), 199 (4), 189 (7), 123 (67). High resolution molecular weight determination, *Mol. Wt.* calcd. for $C_{15}H_{20}O_2$: 232.1463; found: 232.1456.

Methyl (11S)-3,8-dioxo-7αH-eudesma-1,4-dien-12-oate, ***15***

CrO_3 (2.57 g, 25.7 mmol) was added at 0°C portionwise (**slow addition!**) under Ar to a mixture of dry pyridine (5.5 mL) and dry CH_2Cl_2 (30 mL). After stirring this mixture for 4–5 min at 0°C, a solution of **6** (360 mg, 1.3 mmol) in dry CH_2Cl_2 (15 mL) was added. Stirring was then maintained for 6 h at 0°C, after which the reaction

mixture was filtered, washed successively with 0.1 *N* HCl, water, 5% aqueous $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Filtration, evaporation of the solvent *in vacuo*, and column chromatography on silica gel (elution with hexane–EtOAc 1:1) yielded **15** (340 mg, 95%) as a colorless oil, lit. (*7a*) solid mp 95–97°C; $[\alpha]_D^{25}$ −100°, with the expected ir, uv, and mass spectra; ^{1}H nmr, δ (ppm): 6.67 (d, J = 9.8 Hz, H-1), 6.30 (d, J = 9.8 Hz, H-2), 3.72 (s, 3H, COOMe), 3.17 (dd, J = 13.6 and 6.2 Hz, H-6α), 3.01 (qd, J = 7.2 and 5.2 Hz, H-11), 2.83 (tq, J = 13.6 and 1 Hz, H-6β), 2.70–2.60 (m, 1H, H-7), 2.49 (d, J = 13.8 Hz, H-9β), 2.35 (d, J = 13.8 Hz, H-9α), 2.01 (d, 3H, J = 1 Hz, H-15), 1.31 (d, 3H, J = 7.2 Hz, H-13), 1.30 (s, 3H, H-14).

Methyl (11S)-3-oxo-8β-hydroxy-7αH-eudesma-1,4-dien-12-oate, ***16***

Diketoester **15** (330 mg, 1.19 mmol) was dissolved in dry THF (30 mL) and treated at 0°C with $LiAlH(OBu^t)_3$ (960 mg, 3.77 mmol). After stirring for 3 h under Ar at this temperature, the reaction was carefully quenched by addition of 0.5 *N* HCl (25 mL), diluted with brine, and extracted with EtOAc (3 × 40 mL). The organic layer was then washed with water, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and chromatographed on silica gel. Elution with hexane–EtOAc 1:1 gave **16** (280 mg, 84%) as white needles, mp 160–161°C (from hexane–CH_2Cl_2) (lit. (*7a*) oil); $[\alpha]_D^{25}$ −138°, with the expected ir, uv and mass spectra; ^{1}H nmr, δ (ppm): 6.75 (d, J = 9.8 Hz, H-1), 6.17 (d, J = 9.8 Hz, H-2), 4.20 (apparent q, average J = 2.7 Hz, H-8), 3.74 (s, 3H, COOMe), 2.74 (dq, J = 9.3 and 7 Hz, H-11), 2.60–2.40 (m, 2H, H-6α and H-6β), 2.07 (dd, J = 14.4 and 2.4 Hz, H-9β), 1.89 (br s, 3H, H-15), 1.67 (dddd, J = 11.1, 9.3, 5, and 2.7 Hz, H-7), 1.46 (dd, J = 14.4 and 3.4 Hz, H-9α), 1.44 (s, 3H, H-14), 1.23 (d, 3H, J = 7 Hz, H-13).

Further elution led to the recovery of ca. 1.5 mg (4.5%) of the 8α-hydroxyester **6**.

3-Oxo-7,8,11αH-eudesma-1,4-dien-12,8-olide, ***17***a

The hydroxyester **16** (270 mg, 0.97 mmol) was lactonized as described above (**6** → **7** and **10** → **11**) by refluxing in benzene (15 mL) in the presence of CSA (25 mg) for 90 min. Work-up and column chromatography on silica gel (elution with hexane–EtOAc 1:1) yielded ***17a*** (236 mg, 99%) as a white solid, mp 178–179°C (from hexane–CH_2Cl_2) (lit. (*7a*) mp 180–180.5°C); $[\alpha]_D^{25}$ −136° (lit. (*7a*) $[\alpha]_D^{23}$ −117.5°), with the expected ir, uv, and mass spectra; ^{1}H nmr, δ (ppm): 6.77 (d, J = 9.8 Hz, H-1), 6.22 (d, J = 9.8 Hz, H-2), 4.49 (td, J = 4.4 and 1.9 Hz, H-8), 2.92 (quintuplet, J = 6.9 Hz, H-11), 2.79 (dd, J = 13.6 and 5.8 Hz, H-6α), 2.50 (dddd, J = 13.6, 6.9, 5.8, and 4.4 Hz, H-7), 2.48 (dd, J = 15.3 and 1.9 Hz, H-9β), 2.04 (br t, J = 13.6 Hz, H-6β), 1.94 (br s, 3H, H-15), 1.58 (dd, J = 15.3 and 4.4 Hz, H-9α), 1.30 (s, 3H, H-14), 1.29 (d, 3H, J = 6.9 Hz, H-13). Several signals in the reported spectrum (*7a*) appear to have been misassigned.

3-Oxo-11α-phenylseleno-7,8αH-eudesma-1,4-dien-12,8-olide, ***17***b

The published procedure (*7a*) was exactly repeated. It yielded ***17b*** in 49% yield as colorless crystals, mp 214–215°C (from EtOAc) (lit. (*7a*) mp 215–218°C), with the expected ir, uv, and mass spectra; ^{1}H nmr, δ (ppm): 7.70–7.30 (m, 5H, aromatic hydrogens), 6.80 (d, J = 9.9 Hz, H-1), 6.25 (d, J = 9.9 Hz, H-2), 5.08 (m, 1H, H-8), 2.89 (dd, J = 13.5 and 5.7 Hz, H-6α), 2.54 (dd, J = 15.4 and 1.9 Hz, H-9β), 2.46 (ddd, J = 13.5, 5.7, and 4.1 Hz, H-7), 2.16 (br t, J = 13.5 Hz, H-6β), 1.95 (br s, 3H, H-15), 1.64 (s, 3H, H-13), 1.63 (dd, J = 15.4 and 4.7 Hz, H-9α), 1.33 (s, 3H, H-14).

Yomogin, ***2***

The oxidation of ***17b*** was carried out according to the described procedure (*7a*). After crystallization from EtOAc, yomogin **2** was obtained in 33% yield as colorless cubes, mp 206–207°C (lit. (*7a*) mp 210–211°C), with the expected ir, uv, and mass spectra; ^{1}H nmr, δ (ppm): 6.81 (d, J = 9.9 Hz, H-1), 6.28 (d, J = 1 Hz, H-13′), 6.26 (d, J = 9.9 Hz, H-2), 5.76 (d, J = 1 Hz, H-13), 4.51 (apparent q, average J = 4.2 Hz, H-8), 3.20–3.05 (m, 1H, H-7), 3.00 (dd, J = 13.6 and 7 Hz, H-6α), 2.46 (dd, J = 15.3 and 2.6 Hz, H-9β), 2.31 (ddq, J = 13.6, 11, and 1.2 Hz, H-6β), 1.98 (d, 3H, J = 1.2 Hz, H-15), 1.70 (dd, J = 15.3 and 4.7 Hz, H-9α), 1.35 (s, 3H, H-14).

3-Oxo-7,8,11αH-eudesm-4-en-12,8-olide, ***19***

Lactone ***17a*** (210 mg, 0.85 mmol) was dissolved in benzene–ethanol 1:1 (15 mL) and hydrogenated for 14 h under the same conditions as **7** in the presence of Wilkinson catalyst (40 mg). Work-up and column chromatography (elution with hexane–EtOAc 7:3) afforded **19** (201 mg, 95%) as a white solid, mp 103–104°C (from hexane–CH_2Cl_2) (lit. (*7a*) mp 111–112°C); $[\alpha]_D^{25}$ +92° (lit. (*7a*) $[\alpha]_D^{23}$ +130.4°), with the expected ir, uv, and mass spectra; ^{1}H nmr, δ (ppm): 4.52 (apparent q, average J = 2.7 Hz, H-8), 2.90 (quintuplet, J = 7 Hz, H-11), 2.67 (dd, J = 13.9 and 5.8 Hz, H-6α), 2.54 (dddd, overlapped; H-7), 2.55–2.40 (m, 2H, H-2α and H-2β), 2.30 (dd, J = 15.5 and 2.5 Hz, H-9β), 1.96 (tq, J = 13.9 and 1.3 Hz, H-6β), 1.90–1.75 (m, 2H, H-1α/1β), 1.82 (d, 3H, J = 1.3 Hz, H-15), 1.72 (dd, J = 15.5 and 4.4 Hz, H-9α), 1.30 (s, 3H, H-14), 1.28 (d, 3H, J = 7 Hz, H-13).

3,3-Ethanedithio-7,8,11αH-eudesm-4-en-12,8-olide, ***20***

A modification of the published procedure (*7b*) was utilized: Lactone **19** (180 mg, 0.72 mmol), ethanedithiol (0.45 mL, 5.34 mmol), and $BF_3 \cdot OEt_2$ (40 μL) were dissolved in glacial acetic acid (3 mL) and stirred for 4 h at room temperature. The reaction mixture was then poured into water (20 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography on silica gel (elution with hexane–EtOAc 19:1) yielded **20** (206 mg, 87%) as white needles, mp 138–139°C (from hexane–CH_2Cl_2) (lit. (*7b*) mp 141–143°C); $[\alpha]_D^{25}$ +51° (lit. (*7b*) $[\alpha]_D^{23}$ +50.3°), with the expected ir and mass spectra; ^{1}H nmr, δ (ppm): 4.45 (m, 1H, H-8), 3.40–3.20 (m, 4H, thioketal hydrogens), 2.81 (qd, J = 7.2 and 6.2 Hz, H-11), 2.44 (dd, J = 14.2 and 5.8 Hz, H-6α), 2.37 (m, 1H, overlapped, H-7), 2.25–2.10 (m, 2H, H-2α/2β), 2.18 (dd, J = 15.4 and 1.8 Hz, H-9β), 1.93 (d, 3H, J = 1.1 Hz, H-15), 1.80–1.60 (m, 3H, H-1α/1β and H-6β), 1.57 (dd, J = 15.4 and 4.4 Hz, H-9α), 1.22 (d, 3H, J = 7.2 Hz, H-13), 1.14 (s, 3H, H-14).

7,8,11αH-Eudesm-4-en-12,8-olide, ***21****, and 5,7,8,11αH-eudesm-3-en-12,8-olide,* ***22***

Approximately 4 g active W-2 Raney nickel were added at once to a solution of thioketal **20** (195 mg, 0.6 mmol) in 6 mL MeOH. The mixture was stirred for 10 min at room temperature and the reaction was quenched by rapid addition of ethanedithiol (0.2 mL). Work-up as above (**12** → **14**) and column chromatography on silica gel (elution with hexane–EtOAc 9:1) yielded first **21** (81 mg, 57%) as a colorless oil, lit. (17) solid mp 59–62°C; $[\alpha]_D^{25}$ +47° (lit. (17) $[\alpha]_D^{20}$ +29.7°); its enantiomer has been reported to be an oil, $[\alpha]_D$ −53° (11, 19); ^{1}H nmr, δ (ppm): 4.45 (td, J = 4 and 2 Hz, H-8), 2.78 (qd, J = 7.2 and 6.2 Hz, H-11), 2.46 (dd, J = 13.9 and 5.8 Hz, H-6α), 2.29 (dddd, J = 12.2, 6.2, 5.8, and 4 Hz, H-7), 2.13 (dd, J = 15.3 and 2 Hz, H-9β), 2.00–1.65 (m, 3H, H-3α/3β and H-6β), 1.64 (br s, 3H, H-15), 1.54 (dd, J = 15.3 and 4 Hz, overlapped; H-9α), 1.22 (d, 3H, J = 7.2 Hz, H-13), 1.11 (s, 3H, H-14). High resolution molecular weight determination, *Mol. Wt.* calcd. for $C_{15}H_{22}O_2$: 234.1620; found: 234.1618.

Further elution with the same solvent mixture gave 18 mg (13%) of a solid compound, mp 106–107°C (from hexane–EtOAc); $[\alpha]_D^{25}$ +7°, which was assigned structure **22** on the basis of its spectral properties: ir (KBr), ν_{max}: 1765 (s), 1755 (s), 1165 (s) cm^{-1}; ^{1}H nmr at 500 MHz, δ (ppm): 5.36 (m, 1H, H-3), 4.48 (td, J = 4.3 and 1.8 Hz, H-8), 2.79 (quintuplet, J = 7.1 Hz, H-11), 2.39 (dddd, J = 12.4, 7.1, 6.2, and 4.3 Hz, H-7), 2.12 (dd, J = 15.3 and 1.8 Hz, H-9β), 2.10–1.90 (m, 2H, H-2α/2β), 1.88 (br d, $J \simeq$ 13.6 Hz, H-5), 1.74 (ddd, J = 13.6, 6.2, and 2.6 Hz, H-6α), 1.63 (br s, 3H, H-15), 1.44 (dd, J = 12.6 and 6.4 Hz, H-1β), 1.39 (dd, J = 15.3 and 4.3 Hz, H-9α), 1.30 (td, J = 12.6 and 6.5 Hz, H-1α), 1.20 (d, 3H, J = 7.1 Hz, H-13), 1.01 (td, J = 13.6 and 12.4 Hz, H-6β), 0.87 (s, 3H, H-14); ms, m/z (% rel. int.): 234 (M^+, 28), 219 (59), 173 (21), 161 (38), 145 (100). High resolution molecular weight determination, *Mol. Wt.* calcd. for $C_{15}H_{22}O_2$: 234.1620; found: 234.1612. *Anal.* calcd. for $C_{15}H_{22}O_2$: C 76.92, H 9.40; found: C 76.76, H 9.51.

11α-Phenylseleno-7,8αH-eudesm-4-en-12,8-olide, ***23***

A solution of *n*BuLi (0.75 mL of a 1.6 *M* solution in hexane,

1.2 mmol) was added at room temperature under Ar via syringe to a solution of diisopropylamine (0.18 mL, 1.26 mmol) and TMEDA (0.55 mL, 3.61 mmol) in dry THF (2 mL). After stirring for 5 min, the mixture was cooled to −23°C (Dry Ice – CCl_4 bath). Lactone **21** (70 mg, 0.3 mmol) was dissolved in dry THF (2 mL) and added dropwise (5 min) to the cooled LDA/TMEDA solution. After stirring for 1 h at −23°C, a solution of PhSeCl (230 mg, 1.2 mmol) and HMPT (0.2 mL) in dry THF (2 mL) was added dropwise (10 min) via syringe. The reaction mixture was stirred for 1 h at −23°C and quenched at this temperature with 0.5 *N* HCl (2 mL). The reaction mixture was then poured into water (15 mL) and extracted with EtOAc (4 × 15 mL). The organic layer was washed twice with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography of the yellowish oily residue (elution with hexane–EtOAc 19:1) yielded **23** (71 mg, 66% based on recovered **21**) as almost colorless crystals, mp 134–135°C (from hexane–CH_2Cl_2); ir (KBr), ν_{max}: 1765 (s), 1170 (m), 740 (m), 690 (m); ^{1}H nmr, δ (ppm): 7.65–7.25 (m, 5H, aromatic hydrogens), 5.01 (m, 1H, H-8), 2.54 (dd, J = 13.6 and 5.9 Hz, H-6α), 2.27 (ddd, J = 12.4, 5.9, and 4.1 Hz, H-7), 2.16 (dd, J = 15.4 and 4.1 Hz, H-9β), 2.00–1.80 (m, 2H, H-3α/3β), 1.81 (dd, J = 13.6 and 12.4 Hz, H-6β), 1.62 (br s, 3H, H-15), 1.59 (dd, J = 15.4 and 4.4 Hz, H-9α), 1.55 (s, 3H, H-13), 1.10 (s, 3H, H-14). *Anal.* calcd. for $C_{21}H_{26}O_2Se$: C 64.79, H 6.68, Se 20.30; found: C 64.88, H 6.58, Se 20.12.

Further elution with the same solvent mixture led to the recovery of unreacted **21** (7 mg).

1-Deoxyivangustin, 3 and 8αH-eudesma-4,7(11)-dien-12,8-olide, 24

Hydrogen peroxide (0.18 mL of a 30% aqueous solution, ca. 1.6 mmol) was added at 0°C to a solution of **23** (63 mg, 0.16 mmol) and AcOH (20 μL) in THF (1.5 mL). After stirring for 1 h at 0°C, the reaction mixture was poured into 5% aqueous $NaHCO_3$ (8 mL) and extracted with EtOAc (4 × 5 mL). The organic layer was washed several times with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography on silica gel (elution with hexane–EtOAc 9:1) gave first 5 mg of a colorless oil (13%), $[\alpha]_D^{25}$ +46°, identified with 1-deoxyivangustin **3** (lit. (8) $[\alpha]_D^{24}$ +35.2°); lit. $[\alpha]_D$ for the enantiomer (11) is surprisingly different in its absolute value (−119°); ir (film), ν_{max}: 1760 (s), 1260 (m), 1115 (m) cm^{-1}; ^{1}H nmr, δ (ppm): 6.23 (d, J = 2.6 Hz, H-13′), 5.60 (d, J = 2.4 Hz, H-13), 4.49 (apparent q, average J = 6.9 Hz, A-part of a strongly coupled AXX′Y-system; H-8), 3.05 (dtt, J = 10, 7.3, and 2.5 Hz, H-7), 2.80 (dd, J = 13.2 and 7.3 Hz, H-6α), 2.10–1.90 (m, 3H, H-3α/3β and H-6β), 1.74 (d, 2H, J = 6.9 Hz, XX′ part of a AXX′Y-system; H-9α/9β), 1.66 (br s, 3H, H-15), 1.08 (s, 3H, H-14); ms, m/z (% rel. int.): 232 (M^+, 36), 217 (100), 199 (12), 171 (55), 145 (53). High resolution molecular weight determination, *Mol. Wt.* calcd. for $C_{15}H_{20}O_2$: 232.1463; found: 232.1456.

Further elution with the same solvent mixture gave 23 mg (61%) of an unstable colorless oil, $[\alpha]_D^{25}$ −76°, which was assigned structure **24** on the basis of its spectral properties; ir (film), ν_{max}: 1750 (s), 1685 (m), 1680 (m), 1025 (m) cm^{-1}; uv, λ_{max} (log ε_{max}): 216 (3.99), 272 (3.76); ^{1}H nmr, δ (ppm): 4.70 (ddq, J = 9.3, 8.2, and 1.9 Hz, H-8), 3.35 (dq, J = 19.8 and 1 Hz, H-6α), 3.25 (dq, J = 19.8 and 1.9 Hz, H-6β), 2.24 (dd, J = 13.3 and 9.3 Hz, H-9β), 2.05–1.85 (m, 2H, H-3α/3β), 1.83 (td, J = 1.9 and 1 Hz, H-13), 1.65 (q, J = 1 Hz, H-15), 1.41 (dd, J = 13.3 and 8.2 Hz, H-9α), 0.94 (s, 3H, H-14); ms, m/z (% rel. int.): 232 (M^+, 39), 217 (100), 199 (9), 189 (15), 171 (12), 161 (22). High resolution molecular weight determination, *Mol. Wt.* calcd. for $C_{15}H_{20}O_2$: 232.1463; found: 232.1460.

Acknowledgements

We are deeply indebted to Professor D. H. R. Barton, Gif-sur-Yvette, for a generous supply of artemisin and to Professors F. Bohlmann, Berlin, and D. S. Caine, Alabama, for the sending of spectra of natural eudesmanolides. We also thank Dr. M. Spraul, Bruker Company, Karlsruhe, West Germany, for recording an ^{1}H nmr spectrum at 500 MHz.

1. H. M. R. Hoffmann and J. Rabe. Angew. Chem. **97**, 96 (1985); Angew. Chem. Int. Ed. Engl. **24**, 94 (1985).
2. C. H. Heathcock. *In* The total synthesis of natural products. Vol. 2. *Edited by* J. ApSimon. John Wiley & Sons, New York. 1973. Chapt. 2.
3. C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac, and C. T. White. *In* The total synthesis of natural products. Vol. 5. *Edited by* J. ApSimon. John Wiley & Sons, New York. 1983.
4. (*a*) M. Arno, B. Garcia, J. R. Pedro, and E. Seoane. Tetrahedron Lett. 1741 (1983); (*b*) M. Arno, M. Carda, J. A. Marco, and E. Seoane. Chem. Lett. 1021 (1984); (*c*) M. Arno, B. Garcia, J. R. Pedro, and E. Seoane. Tetrahedron, **40**, 5243 (1984); (*d*) M. Arno, B. Garcia, J. R. Pedro, and E. Seoane. An. Quím. Ser. C, **80**, 277 (1984); (*e*) M. Carda, M. Arno, and J. A. Marco. Tetrahedron, **42**, 3655 (1986).
5. T. A. Geissman. J. Org. Chem. **31**, 2523 (1966).
6. D. S. Caine and G. Hasenhuettl. J. Org. Chem. **45**, 3278 (1980).
7. (*a*) K. Yamakawa, K. Nishitani, A. Murakami, and A. Yamamoto. Chem. Pharm. Bull. **31**, 3397 (1983); (*b*) K. Yamakawa, K. Nishitani, and A. Murakami. Chem. Pharm. Bull. **31**, 3411 (1983).
8. F. Bohlmann, P. K. Mahanta, J. Jakupovic, R. C. Rastogi, and A. A. Natu. Phytochemistry, **17**, 1165 (1978).
9. F. Bohlmann, C. Trinks, J. Jakupovic, and S. Huneck. Phytochemistry, **24**, 995 (1985).
10. P. Bhandari and R. P. Rastogi. Indian J. Chem. Sect. B, **22**, 286 (1983).
11. Y. Ohta, N. H. Andersen, and C.-B. Liu. Tetrahedron, **33**, 617 (1977).
12. (*a*) M. Nakazaki and K. Naemura. Tetrahedron Lett. 2615 (1966); (*b*) Bull. Chem. Soc. Jpn. **42**, 3366 (1969).
13. E. Piers and K. F. Cheng. Can. J. Chem. **46**, 377 (1968).
14. M. Sumi. J. Am. Chem. Soc. **80**, 4869 (1958).
15. W. Cocker and M. A. Nisbet. J. Chem. Soc. 534 (1963).
16. A. E. Greene, J.-C. Muller, and G. Ourisson. J. Org. Chem. **39**, 186 (1974).
17. K. Naemura and M. Nakazaki. Tetrahedron Lett. 33 (1969).
18. R. W. Ratcliffe. Org. Synth. **55**, 84 (1976).
19. Y. Asakawa, M. Toyota, T. Takemoto, and C. Suire. Phytochemistry, **18**, 1007 (1979).