Phytochemistry, Vol. 25, No. 4, pp. 891–897, 1986.
Printed in Great Britain.

0031-9422/86 $3.00 + 0.00

EUDESMAN-12,8β-OLIDES AND OTHER TERPENES FROM *ARTEMISIA* SPECIES

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(*Received* 13 *June* 1985)

Key Word Index—*Artemisia iwayomogi*; *A. gmelinii*; *A. santolinifolia*; *A. caerulescens* var. *cretacea*; Compositae; sesquiterpene lactones; eudesmanolides; guaianolides; hydroperoxides; nerolidol derivatives.

Abstract—The aerial parts of *Artemisia iwayomogi* afforded, in addition to already known terpenes, eleven new eudesmanolides whereas four new guaianolides were found in *A. gmelinii*. No sesquiterpene lactones were detected in the aerial parts of *A. santolinifolia* which afforded two new nerolidol derivatives besides several other already known compounds. From *A. caerulescens* var. *cretacea* six eudesmanolides were isolated, one of which has not been reported previously. The structures were elucidated by high field ^{1}H NMR spectroscopy and chemical transformations. The chemotaxonomic significance of sesquiterpene lactones within the section *Abrotanum* and the subgenus *Seriphidium* is briefly discussed.

INTRODUCTION

The large genus *Artemisia*, comprising about 400 species, is divided into four subgenera *Artemisia*, *Seriphidium*, *Tridentatae* and *Dracunculus*. However, more detailed systematic treatments have shown that further infrageneric divisions are not entirely satisfactory (for ref. compare [1–3]). Comparative phytochemical analyses within the genus have shown that the distribution of polyacetylenes, sesquiterpene coumarin ethers, sesamin type lignans and sesquiterpene lactones may contribute to a better understanding of infrageneric relationships [1–5]. Although in the latter class of substances numerous data have already been compiled and reviewed by several authors [e.g. 1, 4, 5], there are still many problems in systematic interpretations because of the great infraspecific variation, structural complexity and the lack of data within several sections and subgenera. The present paper reports on the chemical investigation of three further species of the section *Abrotanum* (subgenus *Artemisia*) and one species of the subgenus *Seriphidium*.

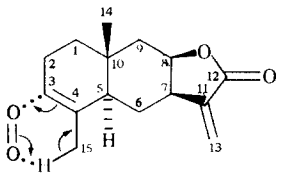
RESULTS AND DISCUSSION

The petrol–ether extracts of the aerial parts of the North Japanese *A. iwayomogi*, belonging to the section *Abrotanum*, series *Vestitae* [6], afforded the monoterpenes α-thujone, camphor, borneol, piperitone, the sesquiterpenes germacrene D, bicyclogermacrene, spathulenol as well as the already known eudesmanolide isotelekin [7] together with eleven new eudesmanolides (**1**–**11**). From the closely related *A. gmelinii* which originated near Vladivostok (U.S.S.R.), in contrast, five guaianolides as well as the monoterpenes α-thujone, camphor and the sesquiterpenes germacrene D, bicyclogermacrene and α-humulene were isolated. Apart from the guaianolide zuurbergenin which so far has only been reported from '*Matricaria*' *zuurbergensis* [8], the guaianolides 1α-peroxy-1-desoxyrupicolin A (**12**) and B (**14**) as well as rupicolin A-acetate (**13**) and rupicolin B-acetate (**15**) have proved to be new, except that the derivatives **12** and **14** were previously isolated as a mixture [9] (^{1}H NMR data: see Table 2).

A. santolinifolia, another member of the series *Vestitae*, has already been investigated [10–12]. The reinvestigation of the aerial parts afforded in addition to known terpenes (see Experimental) two new nerolidol derivatives **16** and **17**, but no sesquiterpene lactones at all. In a corresponding extract from *A. caerulescens* var. *cretacea*, belonging to the subgenus *Seriphidium*, germacrene D, camphor and the six eudesmanolides α-santonin [13], lumisantonin [14, 15], 11-epi-artemin (arsubin) [4], 11-epi-taurin [16], the corresponding 1-hydroxy derivative 11-epi-artesin [16] and the new eudesmanolide **18** were detected, of which the latter could only be separated from the former after acetylation. Taurin has been reported for another provenance of that species [17].

The structure of the eudesmanolide **1**, molecular formula $C_{15}H_{20}O_2$, could be deduced from the ^{1}H NMR spectrum (Table 1) which was in part similar to that of isoalantolactone. Especially the signals of H-6 through H-9 and H-13 were nearly identical. However, the changed position of the double bond clearly followed from the presence of an olefinic proton and an olefinic methyl group. Spin decoupling allowed the assignment of all signals leading to sequences which only agreed with the proposed structure. The stereochemistry at C-5, C-7 and C-8 followed from the couplings observed and from comparison with the data of similar lactones with the same configuration at these centres. Thus compound **1** was a further isomer of alantolactone which surprisingly was not reported previously. However, the enantiomer was isolated from the liverwort *Diplophyllum albicans* [18], of which ^{1}H NMR spectral data agree well with those of compound **1** though the mp differs slightly.

The structure of compound **2** also followed from the



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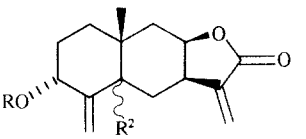
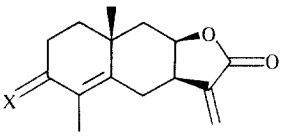
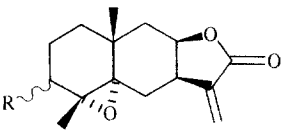


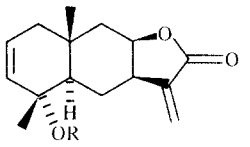
	2	3	4	5
R	OH	H	OH	OH
R^1	αH	αOH	αOH	βOH



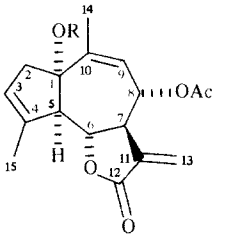
6 X = αOOH,H
7 X = αOH,H
8 X = O



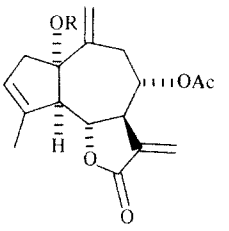
9 R = αOH
10 R = βOH



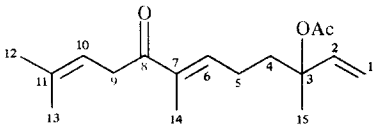
11 R = OH
11a R = H



12 R = OH
13 R = H



14 R = OH
15 R = H



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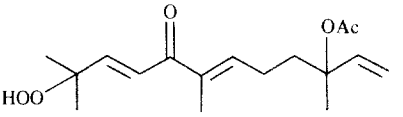
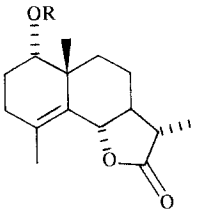


17



18 R = H
19 R = Ac

^{1}H NMR spectral data (Table 1) which were nearly identical with those of isotelekin [7]. However, as in similar cases, the H-3 signal was slightly shifted downfield and a typical hydroperoxide signal at δ7.91 was present. Accordingly, addition of triphenylphosphine afforded isotelekin, while reaction with acetanhydride gave the corresponding acetate. In this case, the usual transformation to the corresponding ketone was not observed. The ^{1}H NMR signals of H-3 and H-5 were shifted downfield in the spectrum of the acetate of compound **2**.

The ^{1}H NMR spectrum of compound **3** (Table 1) was close to that of isotelekin. However, as already followed from the molecular formula the lactone **3** had an additional hydroxyl group which only could be placed at C-5 as the H-6β signal was changed from a three-fold doublet to a double doublet. The stereochemistry was confirmed by NOE difference spectroscopy. Thus clear NOEs were observed between H-14, H-6β and H-9β as well as between H-3 and H-6β.

The ^{1}H NMR spectrum of compound **4** (Table 1) was close to that of compound **3**. However, the presence of a hydroperoxide was indicated by the lowfield singlet. The

Table 1. ^{1}H NMR spectral data of compounds **1–11** ($CDCl_3$, 400 MHz, TMS as internal standard)

	1	**2**	**3**	C_6D_6	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**11a**
H-1α	1.30 *br ddd*	1.52 *ddd*	2.02 *br ddd*	1.87 *br ddd*	*	1.90 *m*	*	1.73 *m*	2.04 *ddd*	1.44 *ddd*	1.08 *m*	1.96 *br dd*	1.92 *br dd*
H-1β	1.45 *br d*	1.32 *ddd*	1.12 *br d*	0.72 *br d*	*	1.34 *br d*	1.36 *m*	1.37 *dt*	1.75 *ddd*			1.90 *m*	1.86 *m*
H-2α	1.96 *m*	1.95 *ddd*	1.85 *m*	1.36 *dddd*	1.90 *m*	1.99 *m*	1.73 *m*	1.93 *dt*	2.46 *ddd*	2.04 *m*	*	5.90 *ddd*	5.61 *ddd*
H-2β	2.07 *dddq*	1.79 *ddd*		1.44 *dddd*				1.73 *m*	2.61 *ddd*				
H-3	5.38 *br s*	4.44 *t*	4.46 *t*	3.81 *t*	4.59 *t*	4.61 *t*	4.22 *br dd*	3.92 *br dd*	—	4.13 *t*	3.86 *t*	5.58 *ddd*	5.52 *ddd*
H-5	1.96 *m*	2.28 *dq*	—	—	—	—	—	—	—	—	—	2.26 *dd*	1.66 *dd*
H-6α		1.76 *ddd*	1.75 *m*	1.63 *dd*	2.41 *dd*	2.01 *dd*	2.79 *dd*	2.76 *dd*	2.22 *br d*	1.87 *m*†	1.59 *dd*	1.89 *ddd*	1.97 *ddd*
H-6β	1.23 *ddd*	1.39 *dd*	1.62 *dd*	1.44 *dd*	1.54 *dd*	2.81 *dd*	1.98 *br dd*	1.97 *br dd*	3.05 *dd*	1.61 *dd*	1.89 *dd*	1.34 *ddd*	1.34 *ddd*
H-7	3.01 *br ddd*	3.01 *br ddd*	3.36 *br ddd*	3.05 *br ddd*	3.35 *br ddd*	3.23 *m*	3.07 *ddddd*	3.07 *ddddd*	3.23 *ddddd*	3.07 *br ddd*	3.19 *br ddd*	3.02 *br ddd*	2.98 *br ddd*
H-8	4.53 *dt*	4.51 *dt*	4.55 *dt*	4.10 *dt*	4.57 *dt*	4.82 *ddd*	4.48 *ddd*	4.51 *ddd*	4.61 *ddd*	4.47 *dt*	4.55 *dt*	4.48 *dt*	4.45 *dt*
H-9α	1.45 *br dd*	1.54 *dd*	2.11 *br dd*	1.91 *br dd*	1.90 *m*	1.81 *dd*	1.73 *m*	1.75 *dd*	1.93 *dd*	2.38 *dd*	1.76 *br dd*	1.61 *br dd*	1.52 *br dd*
H-9β	2.16 *dd*	2.18 *dd*	1.91 *br d*	1.69 *dd*		1.65 *dd*	1.84 *dd*	1.85 *dd*	1.77 *dd*	1.84 *br d*	2.12 *dd*	2.18 *dd*	2.16 *dd*
H-13	6.13 *d*	6.15 *d*	6.15 *d*	6.02 *d*	6.16 *d*	6.34 *d*	6.25 *d*	6.24 *d*	6.37 *d*	6.13 *d*	6.15 *d*	6.13 *d*	6.13 *d*
H-13′	5.60 d	5.60 *d*	5.60 *d*	5.02 *d*	5.61 *d*	5.68 *d*	5.63 *d*	5.61 *d*	5.72 *d*	5.55 *d*	5.59 *d*	5.59 *d*	5.57 *d*
H-14	0.89 *s*	0.83 *s*	0.91 *br s*	0.79 *br s*	1.00 *s*	0.84 *s*	1.08 *s*	1.04 *s*	1.21 *s*	1.11 *s*	1.20 *br s*	1.02 *s*	0.95 *s*
H-15	1.62 *ddq*	5.13 *t*	5.12 *br s*	4.63 *s*	5.48 *s*	5.57 *d*	1.82 *br s*	1.81 *br s*	1.81 *br s*	1.58 *s*	1.39 *s*	1.08 *s*	1.10 *s*
H-15′		4.81 *t*	4.93 *br s*	4.52 *s*	5.25 *s*	5.32 *d*							
OOH	—	7.91 *s*	—	—	8.25 *s*	7.67 *s*	7.30 *s*	—	—	—	—	7.30 *s*	—

*Overlapped multiplets.

†$CDCl_3$–C_6D_6 1.61 *dd* (H-6α), 1.37 *dd* (H-6β).

J (Hz) Compounds **1–4**: 1α, 1β = 1α, 2β ~ 13; 1α, 2α = 1β, 2β ~ 4; 1β, 2α = 2α, 3β = 2β, 3β ~ 3; 6α, 6β = 14; 6α, 7 = 6.5; 6β, 7 = 12; 7, 8 = 8, 9α = 5; 7, 13 = 8, 9β ~ 1.5; 9α, 9β = 15 (compound **2**: 5, 6α = 5, 15 = 1.5; 5, 6β = 13); compound **5**: 1α, 1β = 14; 2α, 3 = 2β, 3 = 2.5; 6α, 6β = 16; 6α, 7 = 2; 6β, 7 = 7.5; 7, 8 = 8; 7, 13 = 3.5; 7, 13′ = 3; 8, 9α = 6; 8, 9β = 11; 9α, 9β = 14; compounds **6** and **7**: 2α, 3 = 2β, 3 ~ 3; 3, 6β = 6β, 15 ~ 1.5; 6α, 6β = 14; 6α, 7 = 7.5; 6β, 7 = 13; 7, 8 = 7.5; 7, 13 = 2; 7, 13′ = 2; 8, 9α = 5; 8, 9β = 8; 9α, 9β = 14; compound **8**: 1α, 1β = 1α, 2β ~ 13; 1α, 2α = 1β, 2β = 5; 1β, 2α = 2; 2α, 2β = 19; 6α, 6β = 6β, 7 = 13; 6α, 7 = 7; 6β, 15 ~ 1.5; 7, 8 = 8.5; 7, 13 = 3; 7, 13′ = 2.5; 8, 9α = 5; 8, 9β = 12; 9α, 9β = 14; compounds **9** and **10**: 1α, 14 = 9α, 14 ~ 0.5; 6α, 6β = 14; 6α, 7 ~ 2; 6β, 7 = 12; 7, 8 = 8, 9α = 5; 7, 13 = 8, 9β ~ 1; 9α, 9β = 15 (compound **9**: 1α, 1β = 1α, 2β = 13; 1α, 2α = 4.5; 2α, 3 = 2β, 3 ~ 2; compound **10**: 2α, 3 = 2β, 3 ~ 8); compounds **11** and **11a**: 1α, 1β = 17; 1α, 2 = 5; 1α, 3 = 1β, 3 ~ 2; 1β, 2 = 3; 2, 3 = 10; 5, 6β = 6α, 6β = 13; 5, 6α = 3; 6α, 7 = 7; 6β, 7 = 12; 7, 8 = 8, 9α = 5; 7, 13 = 8, 9β ~ 1.5; 9α, 9β = 16.

relative position of this group followed from the downfield shift of the H-3 signal, if compared with the shift in **3**. Triphenylphosphine reduction of compound **4** gave a diol which was identical with compound **3**.

Compound **5** was an isomer of **4** as followed from the molecular formula. The ^{1}H NMR spectra (Table 1), however, differed strongly. Thus the couplings of H-8 and H-7 differed considerably. The spectrum was, however, close to that of 5β-hydroxyisoalantolactone [19]. The presence and the configuration of an additional peroxy group at C-3 followed from the lowfield signal at δ7.67 at the chemical shift of H-3 (δ4.61 *t*). The relative position of the oxygen function further followed from the comparison of the couplings of H-6–H-9 which are typically influenced by a 5β-peroxy group [19, 20].

As again followed from the lowfield singlet at δ7.85 compound **6** also was a hydroperoxide. As could be deduced from the results of careful spin decoupling a Δ^4-eudesmanolide was present. Thus a coupling between H-6β and H-15 was observed. As in similar eudesma-4,11-dien-12,8β-olides [19, 21], the couplings observed for H-6–H-9 indicated a changed conformation obviously due to the presence of a 4,5-double bond. The configuration at C-3 followed from the small coupling $J_{2,3}$. On heating of compound **6** with acetanhydride the ketone **8** was obtained which also was isolated as a natural product. Its structure again was deduced from the ^{1}H NMR spectrum (Table 1). All signals were assigned by spin decoupling. NOE difference spectroscopy indicated that the stereochemistry at C-7, C-8 and C-10 was not changed. Clear NOEs were observed between H-14, H-2β and H-9β, between H-15 and H-6β as well as between H-7 and H-8. An enantiomer of **8** has been reported previously from liverworts [22]. The ^{1}H NMR spectral data of a lactone, which is supposed to be the same [23], differed from those of **8** while the ^{13}C NMR data are the same! Lactone **7** was the corresponding 3α-hydroxy derivative as followed from the ^{1}H NMR spectral data (Table 1). Again the typical shift differences for the H-3 signal in the spectra of compounds **6** and **7** were observed.

The molecular formulae and the ^{1}H NMR spectra of **9** and **10** (Table 1) indicated that we were dealing with a pair of isomers. The signals of H-7, H-8 and H-13 were nearly identical with those of isotelekin and compound **2**. However, in both spectra two singlets for methyls at saturated carbons were visible. As in both cases spin decoupling indicated the absence of a proton at C-5, 4,5-epoxides were most likely. The position of a hydroxyl group at C-3 was assumed from biogenetic considerations. This was supported by the presence of W-couplings of H-14 with H-1α and H-9α, excluding a 1α-hydroxyl group. The configuration at C-3 followed from the couplings and that at C-5 was deduced from comparison of the ^{1}H NMR spectra with those of the epimeric 4,5-epoxides obtained from eudesma-4,11-dien-12,8β-olide [19] as a β-epoxide induces a change of the conformation which can be seen from the couplings of H-8. Thus, compounds **9** and **10** only differ in the stereochemistry at C-3. Inspection of a model showed that the downfield shift of the H-9α signal in the spectrum of compound **9**, if compared with that of **10**, can be explained with a deshielding effect of the hydroxyl group. A similar deshielding effect of the 3β-hydroxyl group at H-6β was visible.

The ^{1}H NMR spectrum of compound **11** (Table 1) again indicated the presence of a hydroperoxide (δ7.30 *s*). The presence of a 2,3-double bond could be deduced from the typical three-fold doublets at δ5.90 and 5.58. Triphenylphosphine reduction gave the corresponding alcohol **11a**. A strong downfield shift of H-5α in the spectrum of compound **11** indicated the 4α-position of the peroxy group. The signals of H-6–H-9 and H-13 were similar to those of the other eudesmanolides. Thus, the structure of compound **11** also was established. Most likely all these eudesmanolides are derived from the lactone **1**. As shown in the formula chart, compound **2** could be formed by an ene-reaction with oxygen. Further allylic oxidation and reduction could lead to compounds **2–5**. In a similar way lactone **6** could be formed by reaction with oxygen if H-5 was abstracted and **11** if H-2α participated in this type of reaction.

The ^{1}H NMR spectra (Table 2) of **13** and **15** differed only in some chemical shifts from the corresponding hydroperoxide. As in similar cases the hydroperoxide group causes a downfield shift of the signals of H-5 and H-9 as compared with H-5 and H-9 of compound **13**. In a similar way the chemical shifts of H-2, H-5, H-6 and H-14 in the spectra of **15** and **14** differed. In both cases spin decoupling allowed the assignment of all signals. The observed shift differences for H-5 again support the 1α-position of the oxygen function in all lactones. Certainly, compounds **13** and **15** are formed via the hydroperoxides **12** and **14** starting with zuurbergenin [8] which is itself most likely the precursor of the widespread guaianolides 11,13-dehydromatricarin and matricarin.

The ^{1}H NMR spectrum of compound **16** (see Experimental) indicated the presence of a nerolidyl acetate with a keto group at C-8 as followed from the downfield shift of the H-6 signal and the broad two proton doublet at δ3.35 which was coupled with the olefinic proton at C-10. The latter could be assigned by spin decoupling as two olefinic methyl signals were coupled with this proton. The ^{1}H NMR spectrum of

Table 2. ^{1}H NMR spectral data of compounds **12–15** (400 MHz, $CDCl_3$, TMS as internal standard)

	12	**13**	**14**	**15**
H-2α	2.66 *br d*	2.65 *br d*	2.78 *br s*	2.89 *br d*
H-2β	2.54 *br d*	2.59 *br d*		2.32 *br d*
H-3	5.45 *br s*	5.49 *br s*	5.53 *br s*	5.55 *br s*
H-5	3.29 *br d*	2.82 *br d*	2.89 *br d*	2.70 *br d*
H-6	3.99 *dd*	3.94 *dd*	4.00 *dd*	3.89 *dd*
H-7	3.46 *dddd*	3.50 *dddd*	3.29 *dddd*	3.29 *dddd*
H-8	5.36 *ddq*	5.32 *ddq*	4.89 *ddd*	4.93 *ddd*
H-9α	5.65 *dq*	5.47 *dq*	2.73 *dd*	2.68 *dd*
H-9β			2.68 *dd*	2.55 *dd*
H-13	6.31 *d*	6.29 *d*	6.27 *d*	6.23 *d*
H-13′	5.72 *d*	5.69 *d*	5.74 *d*	5.65 *d*
H-14	1.90 *t*	1.93 *br s*	5.33 *br s*	5.40 *br s*
H-14′			5.14 *br s*	5.14 *br s*
H-15	1.93 *br s*	1.92 *br s*	1.86 *br s*	1.92 *br s*
OAc	2.18 *s*	2.15 *s*	2.16 *s*	2.16 *s*
OOH	7.68 *s*		7.66 *s*	

J (Hz): Compounds **12** and **13**: 2α,2β = 17; 5,6 = 11; 6,7 = 9; 7,8 = 12; 7,13 = 3.3; 7,13′ = 2.9; 8,9 = 3; 8,14 = 9,14 ~ 1.5; compounds **14** and **15**: 2α,2β = 17; 5,6 = 10.5; 6,7 = 9.5; 7,8 = 10.5; 7,13 = 3.5; 7,13′ = 3; 8,9α = 6.5; 8,9β = 5; 9α,9β = 14.

compound **17** (see Experimental) showed the typical signal of hydroperoxide (δ 7.82 *br s*), the doublets of an *E*-orientated double bond and three singlets for methyls at saturated carbons. Accordingly, the structure could be assigned as the remaining signals were nearly identical with those of compound **16** which most likely is the precursor of **17**. The corresponding 11-hydroxy derivative was also reported from another batch of *A. santolinifolia* collected in Mongolia [12].

The structure of compound **18** followed from the ^{1}H NMR spectrum and from that of the corresponding acetate **19** (see Experimental). As expected, the H-1 signals in these spectra showed small couplings, while those of the epimers were typical for an axial H-1.

Since the available sesquiterpene lactone data on the section *Abrotanum* are very sparse and are mainly based on a few New World representatives [4, 5], the present results may be of some systematic relevance. Within *Artemisia* the occurrence of eudesman-12,8β-olides appears to be restricted, and so far they have only been reported in seven species mainly belonging to the sections *Artemisia* and *Absinthium* [4, 5, 18, 20, 24–27]. All three sections are grouped together in the subgenus *Artemisia* which from the phylogenetic viewpoint most likely represents the most ancient group within the genus. However, as already shown by Appendino *et al.* [20], infraspecific variation with eudesman-12,6α-olides is also to be expected. Different trends towards eudesmanolides and guaianolides in the closely related *A. gmelinii* and *A. iwayomogi* (in ref. [6] even regarded as synonyms) as well as the lack of sesquiterpene lactones in *A. santolinifolia*, belonging to the same series, points to great variability within the section *Abrotanum*. On the other hand, *A. caerulescens* var. *cretacea*, containing santonin and related eudesman-12,6α-olides clearly fits in with other collections of this species and other members of the subgenus *Seriphidium* (see ref. [4]). Further and more detailed studies within the subgenus *Artemisia* will show to what extent sesquiterpene lactone patterns can contribute to a more natural arrangement within this group.

EXPERIMENTAL

Plant material was grown from achenes received from various botanical gardens, as well as from wild collection, and cultivated under field conditions in the Botanical Garden of the University of Vienna. [*A. iwayomogi* Kitam. (AR-807; Hokkaido, Prov. Hiyama, Japan; coll. Koji Ito), *A. gmelinii* Web. ex Stechm. (AR-880; Botanical Garden of Vladivostok, U.S.S.R.), *A.* santolinifolia Turcz. ex Bess. (AR-1126; Botanical Garden of Dushanbe, Horog, U.S.S.R.), *A. caerulescens* L. var. *cretacea* Fiori (AR-1089; Botanical Garden of Siena, Italy)]. Voucher specimens are deposited at the herbarium of the Institute of Botany, University of Vienna (WU).

Air dried aerial parts were extracted with Et_2O–petrol (1:2) at room temp., and the resulting extracts were separated as reported previously [28]. Known compounds were identified by comparing the 400 MHz ^{1}H NMR spectra with those of authentic material.

Artemisia iwayomogi (162 g). CC silica gel afforded four fractions: 1 (petrol), 2 (Et_2O–petrol, 1:10 and 1:3), 3 (Et_2O–petrol, 1:1 and Et_2O) and 4 (Et_2O–MeOH, 9:1). TLC of fraction 1 (silica gel, PF 254, petrol) gave 20 mg germacrene D and 2 mg bicyclogermacrene. TLC of fraction 2 (Et_2O–petrol, 1:10) gave 20 mg α-thujone and 20 mg camphor. TLC of fraction 3 (Et_2O–petrol, 1:1) gave a broad band (R_f 0.65) which by repeated TLC (C_6H_6–$CHCl_3$–Et_2O, 9:9:2) gave 4 mg **1** (R_f 0.65), 2 mg piperitone (R_f 0.55), 3 mg spathulenol (R_f 0.45) and 5 mg borneol (R_f 0.35). TLC of fraction 4 (Et_2O–petrol, 3:1) gave two broad bands (4/1 and 4/2). HPLC (always RP 8, flow rate 3 ml/min, *ca* 100 bar, MeOH–H_2O, 13:7) gave 1.5 mg **4** (R_t 2.6 min), 6 mg **11** (R_t 3.1 min), 10 mg **2** (R_t 3.7 min) and 4 mg **6** (R_t 4.7 min). Repeated TLC of 4/2 (C_6H_6–$CHCl_3$–Et_2O, 1:1:1 + 0.5% MeOH, three developments) gave four bands (4/2/1–4/2/4). HPLC of 4/2/1 (MeOH–H_2O, 13:7) gave 2 mg **8** (R_t 1.8 min). HPLC of 4/2/2 (same solvent) gave 8 mg isotelekin (R_t 2.5 min). HPLC of 4/2/3 (MeOH–H_2O, 3:2) gave 1 mg **5** (R_t 2.5 min), 2 mg **9** (R_t 2.5 min), 1 mg **3** (R_t 3.5 min), 2 mg isotelekin (R_t 4.5 min). HPLC of 4/2/4 (MeOH–H_2O, 3:2) gave 0.5 mg **10** (R_t 1.7 min), 4 mg **3** (R_t 3.6 min) and 3 mg **7** (R_t 6.3 min). All compounds were homogeneous by HPLC and TLC in different solvent mixtures.

Eudesman-4,11-*dien*-12,8β-*olide* (**1**). Colourless crystals, mp 70°; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone); MS *m/z* (rel. int.): 232.146 $[M]^+$ (47) (calc. for $C_{15}H_{20}O_2$: 232.146), 217 $[M-Me]^+$ (100), 171 (26), 145 (23), 131 (23), 121 (26); $[\alpha]_D$ = +98° ($CHCl_3$; *c* = 0.11).

2α-*Peroxyisoalantolactone* (**2**). Colourless crystals, mp 148°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (OOH), 1760 (γ-lactone); MS *m/z* (rel. int.): 264.136 $[M]^+$ (0.5) (calc. for $C_{15}H_{20}O_4$: 264.136), 231 $[M-OOH]^+$ (100), 213 (24), 185 (57), 119 (88); $[\alpha]_D$ = +93° ($CHCl_3$; *c* = 0.48). Compound **2** (5 mg) was heated in 0.5 ml Ac_2O for 1 hr at 70°. TLC (Et_2O–petrol, 3:1) gave 2 mg **2** acetate, colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3080, 910 (C=CH_2), 1780 (γ-lactone, OAc); MS *m/z* (rel. int.): 306.147 $[M]^+$ (0.5) (calc. for $C_{17}H_{22}O_5$: 306.147), 264 $[M-ketene]^+$ (2), 246 $[M-HOAc]^+$ (22), 231 $[246-Me]^+$ (27), 185 (50), 119 (83), 91 (100); ^{1}H NMR ($CDCl_3$): 4.67 (*t*, H-3), 2.43 (*dq*, H-5), 1.72 (*ddd*, H-6α), 2.03 s (OAc) (remaining signals as in **2**).

3α,5α-*Dihydroxyisoalantolactone* (**3**). Colourless crystals, mp 178°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH), 3090, 910 (C=CH_2), 1760 (γ-lactone); MS *m/z* (rel. int.): 264.136 $[M]^+$ (1) (calc. for $C_{15}H_{20}O_4$: 264.136), 246 $[M-H_2O]^+$ (100), 231 $[246-Me]^+$ (17), 228 $[246-H_2O]^+$ (27), 218 $[246-CO]^+$ (46), 203 $[218-Me]^+$ (50); $[\alpha]_D$ = +159° ($CHCl_3$; *c* = 0.15).

3α-*Peroxy*-5α-*hydroxyisoalantolactone* (**4**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1760 (γ-lactone); MS *m/z* (rel. int.): 262.121 $[M-H_2O]^+$ (10) (calc. for $C_{15}H_{18}O_4$: 262.121), 246 $[M-H_2O_2]^+$ (11), 228 $[246-H_2O]^+$ (5), 55 (100). To 1 mg **4** in 0.5 ml $CDCl_3$ 5 mg triphenylphosphine was added. After 5 min complete conversion to **3** could be observed in the ^{1}H NMR.

3α-*Peroxy*-5β-*hydroxyisoalantolactone* (**5**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1765 (γ-lactone); MS *m/z* (rel. int.): 262.121 $[M-H_2O]^+$ (12) (calc. for $C_{15}H_{18}O_4$: 262.121), 246 $[M-H_2O]^+$ (14), 228 $[246-H_2O]^+$ (7), 55 (100).

3α-*Peroxyeudesma*-4,11-*dien*-12,8β-*olide* (**6**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3540 (OOH), 1760 (γ-lactone); MS *m/z* (rel. int.): 264.136 $[M]^+$ (0.6) (calc. for $C_{15}H_{20}O_4$: 264.136), 246 $[M-H_2O]^+$ (17), 231 $[M-OOH]^+$ (100), 213 $[231-H_2O]^+$ (14), 185 (22), 129 (60), 91 (61); $[\alpha]_D$ = +90° ($CHCl_3$, *c* = 0.36). Compound **6** (4 mg) was heated in 0.5 ml Ac_2O for 1 hr at 70°. TLC (Et_2O) gave 3 mg **8** (R_f 0.70), colourless crystals, mp 156°; identical with the natural product.

3α-*Hydroxyeudesma*-4,11-*dien*-12,8β-*olide* (**7**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH), 1765 (γ-lactone); MS *m/z* (rel. int.): 248.141 $[M]^+$ (33) (calc. for $C_{15}H_{20}O_3$: 248.141), 233 $[M-Me]^+$ (24), 230 $[M-H_2O]^+$ (83), 215 $[230-Me]^+$ (24), 91 (100).

3-*Oxo-eudesma*-4,11-*dien*-12,8β-*olide* (**8**). Colourless crystals, after recrystallization mp 170°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (γ-lactone), 1660 (C=CC=O); MS *m/z* (rel. int.): 246.126 $[M]^+$ (84) (calc. for $C_{15}H_{18}O_3$: 246.126), 231 $[M-Me]^+$ (21), 218 $[M-CO]^+$ (30),

204 $[M-C_2H_2O]^+$ (48), 91 (86), 53 (100); $[\alpha]_D = +142°$ ($CHCl_3$; $c = 0.05$).

3α-Hydroxy-4α,5α-epoxyeudesm-11-en-12,8β-olide (**9**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 1765 (γ-lactone); MS *m/z* (rel. int.): 264.136 $[M]^+$ (0.3) (calc. for $C_{15}H_{20}O_4$: 264.136), 246 $[M-H_2O]^+$ (1.2), 181 (32), 84 (100); $[\alpha]_D = +140°$ ($CHCl_3$; $c = 0.18$).

3β-Hydroxy-4α,5α-epoxyeudesm-11-en-12,8β-olide (**10**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1760 (γ-lactone); MS *m/z* (rel. int.): 264.136 $[M]^+$ (1) (calc. for $C_{15}H_{20}O_4$: 264.136), 246 $[M-H_2O]^+$ (6), 181 (41), 84 (100); $[\alpha]_D = +250°$ ($CDCl_3$; $c = 0.05$)

4α-Peroxy-eudesma-2,11-dien-12,8β-olide (**11**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OOH), 1760 (γ-lactone); MS *m/z* (rel. int.): 264.136 $[M]^+$ (0.3) (calc. for $C_{15}H_{20}O_4$: 264.136), 231 $[M-OOH]^+$ (100), 157 (92), 119 (90), 91 (66); $[\alpha]_D = +24°$ ($CHCl_3$; $c = 0.46$).To 3 mg **11** in 0.5 ml $CDCl_3$ 10 mg triphenyl phosphine was added. After 5 min the ^1H NMR spectrum had changed to that of **11a**, colourless oil; MS *m/z* (rel. int.): 248.141 $[M]^+$ (20) (calc. for $C_{15}H_{20}O_3$: 248.141), 233 $[M-Me]^+$ (100), 183 (90).

The extract of *Artemisia gmelinii* (373 g) was separated by CC silica gel into four fractions: 1 (petrol), 2 (Et_2O–petrol, 1:10 and 1:3), 3 (Et_2O–petrol, 1:1) and 4 (Et_2O and Et_2O–MeOH, 10:1). TLC (silica gel, $AgNO_3$ coated, petrol) of fraction 1 gave 30 mg germacrene D, 3 mg α-humulene and 12 mg bicyclogermacrene. TLC of fraction 2 (Et_2O–petrol, 1:3) gave 80 mg camphor and 100 mg α-thujone. TLC of fraction 3 (Et_2O–petrol, 1:1) gave 10 mg zuurbergenin and TLC of fraction 4 (Et_2O–petrol, 3:1) gave two broad bands (4/1 and 4/2). HPLC (RP 8, MeOH–H_2O, 13:7) of 4/1 gave 5 mg **12** (R_t 5.2 min) and 3 mg **14** (R_t 4.2 min). HPLC of 4/2 (same conditions) gave after TLC ($CHCl_3$–C_6H_6–Et_2O, 1:1:1, R_f 0.45) 15 mg **13** (R_t 3.6 min) and after TLC ($CHCl_3$–C_6H_6–Et_2O, 1:1:1, R_f 0.45) 10 mg **15** (R_t 2.9 min).

Rupicolin A-8-O-acetate (**13**). Colourless crystals, mp 150°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590 (OH), 1767 (γ-lactone), 1745, 1240 (OAc); MS *m/z* (rel. int.): 304.131 $[M]^+$ (3) (calc. for $C_{17}H_{20}O_5$: 304.131), 244 $[M-HOAc]^+$ (22), 165 (40), 148 (76), 120 (100), 91 (31); $[\alpha]_D = +102°$ ($CHCl_3$; $c = 0.2$).

Rupicolin B-8-O-acetate (**15**). Colourless crystals, mp 144°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1765 (γ-lactone); MS *m/z* (rel. int.): 304.131 $[M]^+$ (8) (calc. for $C_{17}H_{20}O_5$: 304.131), 244 $[M-HOAc]^+$ (100); $[\alpha]_D = +221°$ ($CHCl_3$; $c = 0.18$).

The extract (Et_2O–petrol, 1:2) of the aerial parts (318 g) of *Artemisia santolinifolia* (voucher AR 1126) gave by CC silica gel three fractions: 1 (petrol), 2 (Et_2O–petrol, 1:10 and 1:3) and 3 (Et_2O). TLC of fraction 1 ($AgNO_3$ coated silica gel, Et_2O–petrol, 1:100) gave 10 mg α-curcumene, 40 mg α-zingiberene and 10 mg germacrene D. TLC of fraction 2 (Et_2O–petrol, 1:3) afforded 200 mg ascaridol and 5 mg bornyl acetate. TLC of fraction 3 (Et_2O–petrol, 1:1) gave two bands (3/1 and 3/2). TLC of 3/1 (Et_2O–petrol, 1:3) gave a mixture which could be separated by repeated TLC (Et_2O–petrol, 1:10, two developments) affording 3 mg **16** (R_f 0.45), 2 mg bisabolol (R_f 0.58) and 8 mg phytol (R_f 0.55) which was purified as its acetate (Ac_2O, 70°). HPLC (RP 8, MeOH–H_2O, 3:1) of 3/2 gave 12 mg **17** (R_t 3.3 min).

8-Oxo-nerolidol acetate (**16**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1750 (OAc), 1690 (C=CC=O); MS *m/z* (rel. int.): 278.173 $[M]^+$ (0.5) (calc. for $C_{17}H_{26}O_3$: 278.173), 218 $[M-HOAc]^+$ (3), 149 $[218-C_5H_9]^+$ (100), 121 $[149-CO]^+$ (88), 93 $[121-C_2H_4]^+$ (82), 69 $[C_5H_9]^+$ (64); ^1H NMR ($CDCl_3$): 5.18 (*d*, H-1t), 5.16 (*d*, H-1c), 5.97 (*dd*, H-2), 2.03 (*dt*, H-4), 1.89 (*dt*, H-4′), 2.25 (*dt*, H-5), 6.60 (*br t*, H-6), 3.35 (*br d*, H-9), 5.30 (*br t*, H-10), 1.74 (*br s*, H-12), 1.63 (*br s*, H-13), 1.76 (*br s*, H-14), 1.57 (*s*, H-15), 2.02 (*s*, OAc) [*J* (Hz): 1t,2 = 17; 1c,2 = 11; 4,4′ = 15; 4,5 = 5,6 = 8; 9,10 = 6.5].

11-Peroxy-8-oxo-9,10E-dehydro-10,11-dihydronerolidol acetate (**17**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3550 (OOH), 1745, 1250 (OAc), 1670, 1625 (C=CC=O); MS *m/z* (rel. int.): 277.180 $[M-OOH]^+$ (3) (calc. for $C_{17}H_{25}O_3$: 277.180), 217 $[277-HOAc]^+$ (37), 149 $[217-C_5H_8]^+$ (61), 121 $[149-CO]^+$ (72), 93 $[121-C_2H_4]^+$ (100); $[\alpha]_D = -3°$ ($CHCl_3$; $c = 1.2$); ^1H NMR ($CDCl_3$): 5.20 (*d*, H-1t), 5.17 (*d*, H-1c), 5.96 (*dd*, H-2), 2.09 (*dt*, H-4), 1.92 (*dt*, H-4′), 2.28 (*dt*, H-5), 6.63 (*tq*, H-6), 6.72 (*d*, H-9), 6.82 (*d*, H-10), 1.40 (*s*, H-12 and H-13), 1.83 (*br s*, H-14), 1.57 (*s*, H-15), 2.01 (*s*, OAc), 7.82 (*s*, OOH) [*J* (Hz): 1t,2 = 17; 1c,2 = 11; 4,4′ = 15; 4,5 = 5,6 = 8; 6,14 = 1; 9,10 = 15].

The aerial parts of *Artemisia caerulescens* var. *cretacea* were extracted with Et_2O–petrol (1:2) and the resulting extract was separated first by CC silica gel. The fractions obtained were combined as follows: 1 (petrol), 2 (Et_2O–petrol, 1:1 and Et_2O) and 3 (Et_2O–MeOH, 9:1). TLC (silica gel, PF 254) of fraction 1 gave 2 mg germacrene D, TLC of fraction 2 (Et_2O–petrol, 1:1) gave 5 mg 11-epi-taurin (R_f 0.25) and 10 mg camphor (R_f 0.75).TLC of fraction 3 gave two bands (3/1 R_f 0.35 and 3/2 R_f 0.20). HPLC of 3/1 (RP 8, MeOH–H_2O, 13:7) gave 2 mg lumisantonin (R_t 3.3 min) and 6 mg 11-epi-artesin and 1,11-bis-epi-artesin (**18**) (*ca* 4:3). Acetylation (Ac_2O, 60°, 1 hr) gave after TLC (Et_2O–petrol, 1:1) 2 mg 11-epi-artesin acetate (R_f 0.52) and 1.5 mg **19** (R_f 0.47). HPLC of 3/2 (same conditions as above) gave 2 mg artemin (R_t 2.2 min) and 3 mg α-santonin (R_t 3.6 min).

1,11-Bis-epi-artesin (**18**). Colourless gum, not separated from 11-epi-artesin; ^1H NMR ($CDCl_3$): 3.49 (*dd*, H-1, *J* = 5, 2 Hz), 4.55 (*dtq*, H-6, *J* = 12, 1, 1 Hz), 1.54 (*dddd*, H-7, *J* = 12, 12, 12, 3.5 Hz), 2.26 (*dq*, H-11, *J* = 12, 7 Hz), 1.21 (*d*, H-13, *J* = 7 Hz), 1.14 (*s*, H-14), 1.87 (*br s*, H-15); Acetate **19**: Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone), 1750 (OAc); MS *m/z* (rel. int.): 292.167 $[M]^+$ (4) (calc. for $C_{17}H_{24}O_4$: 292.167), 232 $[M-HOAc]^+$ (100), 217 $[231-Me]^+$ (27); ^1H NMR ($CDCl_3$): 4.76 (*dd*, H-1, *J* = 5, 2 Hz), 2.15 (*m*, H-2), 2.03 (*m*, H-2′), 4.57 (*dtq*, H-6, *J* = 12, 1, 1 Hz), 1.54 (*dddd*, H-7, *J* = 12, 12, 12, 3.5 Hz), 2.27 (*dq*, H-11, *J* = 12, 7 Hz), 1.23 (*d*, H-13, *J* = 7 Hz), 1.17 (*s*, H-14), 1.88 (*br s*, H-15), 2.08 (*s*, OAc).

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