New Eremophilane Sesquiterpenes from a Rhizome Extract of *Petasites hybridus*

by **Antje Bodensieck**, **Olaf Kunert**, **Ernst Haslinger**, and **Rudolf Bauer***

Institute of Pharmaceutical Sciences, Karl-Franzens University of Graz, A-8010 Graz
(phone: +43-316-380-8700; fax: +43-316-380-9860; e-mail: rudolf.bauer@uni-graz.at)

A total of 21 natural products, **1**–**21**, were isolated from a supercritical CO_2 extract of the rhizomes of *Petasites hybridus*. Thereby, seven new eremophilane (=(1*S*,4a*R*,7*R*,8a*R*)-decahydro-1,8a-dimethyl-7-(1-methylethyl)naphthalene) sesquiterpenes, compounds **4**, **5**, **9**, **11**, **12**, **15**, and **17**, were identified. The new constituent 9-hydroxyisobakkenolide (**15**) is the first representative of a group of compounds closely related to the well-known, but rare, bakkenolides. Tsoongianolide B (**18**) and its degradation product ligularenolide (**19**) were found as new *Petasites* constituents as well. The known eremophilanolide **2** was isolated from a plant source for the first time and the oxofuranopetasin **16** was isolated for the first time from the rhizomes of *P. hybridus*, together with eight other known compounds. The C(8)-epimeric 2-[(tigloyl)oxy]eremophilanolides **3** and **8** could clearly be differentiated. All structures were established by extensive 1D- and 2D-NMR experiments (*Tables 1–3*), and confirmed by in-depth GC/MS and HPLC/MS experiments.

Introduction. – *Petasites hybridus* (L.) GAERTN., MEY. et SCHERB. (Asteraceae, tribe Senecioneae) is native to Europe and Northwest Asia, and has been introduced to North America. Characteristic features are a strange, aromatic smell and short, bulbous rhizomes. Meter-long runners allow the formation of big colonies. *P. hybridus* (butterbur) is traditionally used against spasms of the gastrointestinal tract, headache, diseases of the respiratory tract, and externally for support of wound healing and against malignant ulcers [1]. Modern pharmacological investigations started with *Bucher*'s experiments concerning the antispasmodic activity of *P. hybridus* extracts in isolated guinea pig bowels [2]. Perennial allergic rhinitis and the preventive treatment of migraine are more-recent indications for butterbur extracts [3][4].

In the mid-1950s, two Swiss groups isolated sesquiterpenes of the eremophilane type from butterbur rhizomes for the first time [5][6]. *Novotný et al.* [7] described a petasin and a furan-chemovar of butterbur. The furanoeremophilanes of the latter are predominantly oxidized at C(9), less frequently at C(3), and often at both C(2) and C(9) [8]. In the course of our ongoing investigations concerning the anti-inflammatory activities of *P. hybridus*, we found that COX-2 inhibition is independent of the petasin content [9]. Therefore, we focused our investigations on a commercial CO_2 'spissum' extract of subterranean plant material belonging to the furan-chemovar type, which is rich in furanoeremophilanes and their transformation products, eremophilane lactones.

Herein, we report on the isolation and structure elucidation of a series of eremophilane sesquiterpenes, **1**–**21**[1]), of the rhizomes of *P. hybridus*. In addition, we will provide a basis for the efficient phytochemical analysis of *P. hybridus* extracts by means of high-performance liquid chromatography diode-array-detection mass spectrometry (HPLC-DAD/MS).

Results and Discussion. – A commercial solvent-free 'spissum' extract of *P. hybridus* rhizomes, prepared with supercritical CO_2, was fractionated by vacuum liquid chromatography (VLC) on silica gel. The combined fractions *Fr. III* and *Fr. IV* were further fractionated by column chromatography on silica gel. All sub-fractions were allowed to crystallize. Mother liquors or crystals, respectively, were submitted to either preparative or semi-preparative HPLC, which afforded compounds **1**–**13** and **15**–**21**. Compound **14** was isolated by column chromatography on silica gel. Compounds **2**, **4**, **5**, **9**, **11**, **12**, **15**, and **17** were isolated for the first time from a natural source. Their ^{1}H- and ^{13}C-NMR data are given in *Tables 1–3*.

The isomeric compounds **1** and **2** were obtained as a whitish, viscous mass in a ratio of *ca*. 3:10. Their molecular formula was deduced as $C_{20}H_{28}O_4$ by EI-MS (*m*/*z* 332.3 (M^+)) and ESI-MS (*m*/*z* 333.2 ($[M+H]^+$)). The ^{1}H- and ^{13}C-NMR spectra of **1** and **2** (*Table 1*), in combination with the MS data, indicated that they were eremophilanolides with different side chains.

The HMBC and HSQC spectra of **1** and **2** showed 20 C-atoms: five Me, four CH_2, and five CH groups, and six quaternary C-atoms. The ^{13}C-NMR data of the sesquiterpene skeletons were in perfect agreement with the published data of '2-(angeloyloxy)-8α-H-eremophilanolide' (=(8*R*)-2-[(angeloyl)oxy]eremophil-7(11)-en-12,8-olide; **1**) [10]. As *Naya et al.* [11] and *Siegenthaler* [10] stated, the 8α-epimers of eremophilane lactones can be clearly distinguished from the 8β-epimers by the chemical shifts of the Me(14) and Me(15) groups[1]). In skeletons with an H_α–C(8), a 'non steroid-like' conformation is stabilized (*Figure*), and the H-atoms of the Me(15) group resonate at higher field than those of Me(14). In contrast, a 'steroid-like' conformation is stabilized in skeletons with a H_β–C(8), and, consequently, Me(14) resonates at higher field. Thus, the observed ^{1}H-NMR chemical shifts of Me(15) (δ(H) 0.87) and Me(14) (δ(H) 1.13) clearly pointed to 8α-H-eremophilanolides in the case of **1** and **2**, more precisely, to *cis*-decalin structures with Me groups at positions 4 and 5, as well as a C_3 chain at position 7. The side chains in **1** and **2** were identified as methylated but-2-enoates. Analysis of the NMR data and comparison with published data [10][12] finally revealed that an angeloyl (=(*Z*)-2-methylbut-2-enoyl; Ang) and a senecioyl (=3-methylbut-2-enoyl; Sen) moiety was at the O-atom in 2-position of **1** and **2**, respectively. Thus, the new compound **2** was identified as (8*R*)-2-[(senecioyl)oxy]eremophil-7(11)-en-12,8-olide.

This is the first report of a 2-[(senecioyl)oxy]-8α-H-eremophilanolide from a plant. *Kitahara et al.* [13] reported the synthesis of 2β-[(senecioyl)oxy]eremophilenolide [13], and *Siegenthaler* [10] isolated the 8β-H epimer from *P. hybridus* rhizomes [10].

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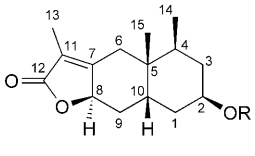
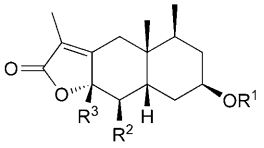
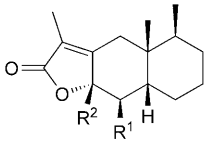
[1]) Please, be aware that the atom numbering of Me(14) and Me(15) in this publication follows the IUPAC recommendation RF-4.5, URL: http://www.chem.qmul.ac.uk/iupac/sectionF/RF45n6.html (December 12, 2006), and therefore differs from numbering in previous publications.



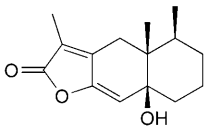
1 R = Ang
2 R = Sen
3 R = Tig
4 R = Met
5 R = Isobutanoyl



	R^1	R^2	R^3
6	Ang	H	H
7	Sen	H	H
8	Tig	H	H
9	Met	H	H
10	**A**	H	H
11	Ang	OH	H
12	Ang	OH	OH



13 R^1 = H, R^2 = OH
14 R^1 = H, R^2 = H



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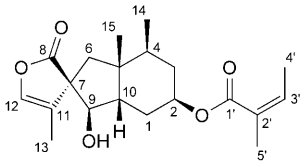

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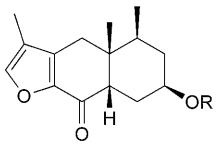
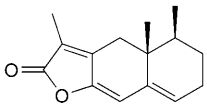
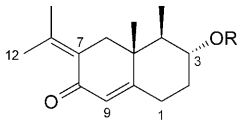


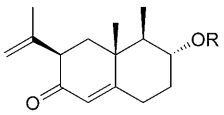
16 R = Ang
17 R = Sen



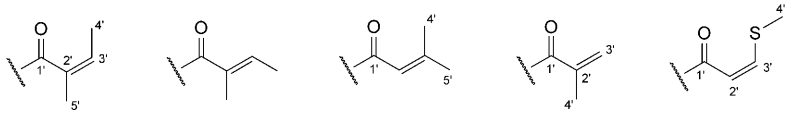
19



20 R = **A**



21 R = **A**



Angeloyl (Ang) | Tigloyl (Tig) | Senecioyl (Sen) | Methacroyl (Met) | **A**

Compound **3** was isolated as a whitish, viscous mass. Its molecular formula was determined by EI-MS (*m/z* 332.3 (M^+)) and ESI-MS (*m/z* 333.2 ($[M+H]^+$)) as $C_{20}H_{28}O_4$. The NMR data of **3** (*Table 1*) indicated that this constituent was an isomer of **1** and **2**, with a tigloyl (=(*E*)-2-methylbut-2-enoyl; Tig) residue instead of a Ang or Sen moiety. The synthesis of **3** has been mentioned by *Kitahara et al.* [13], however, no spectroscopic data were provided by the authors. Therefore, (8*R*)-2-[(tigloyl)oxy]-eremophil-7(11)-en-12,8-olide (**3**) is a new natural product.

Table 1. *^{1}H- and ^{13}C-NMR Data of* **2**–**5**. At 600/150 MHz, resp. in (D_6)acetone (**2**, **3**, **5**) or in $CDCl_3$ (**4**) at 25°; δ in ppm, J in Hz. Asterisks (*) indicate interchangeable assignments.

Position	**2**		**3**		**4**		**5**	
	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)
1	32.1*	1.80*, 2.03*	32.8	1.79, 2.06 (2*m*)	32.1	2.03, 1.85 (2*m*)*	32.9	2.13, 1.74 (2*m*)
2	69.2	5.21	70.7	5.14 (*m*)	70.0	5.20 (*m*)	70.5	5.08
3	32.2*	1.85*, 2.17*	32.8	1.79, 2.13 (2*m*)	32.1	2.03, 1.85 (2*m*)*	32.7	2.06, 1.74 (2*m*)
4	37.3	1.69 (*m*)	38.1	1.70 (*m*)	37.1	1.66 (*m*)	38.1	1.69 (*m*)
5	39.3	–	39.8	–	39.4	–	40.0	–
6	33.7	2.19, 2.70 (2*d*, J=13.8 each)	34.0	2.90, 2.28 (2*d*, J=14.4 each)	33.7	2.70, 2.19 (2*d*, J=13.8 each)	34.0	2.87, 2.27 (2*d*, J=14.4 each)
7	161.9	–	163.4	–	162.0	–	163.4	–
8	77.7	4.83 (*dd*, J=6.6)	78.1	4.93	77.5	4.82 (*dd*, J=11.1, 6.7)	78.0	4.91
9	34.6	1.67 (*t*, J=12), 2.14 (*d*, J=12)	35.6	1.61, 2.11 (2*m*)	34.6	2.14, 1.66 (2*m*)	35.5	2.09, 1.16 (2*m*)
10	31.3	2.13 (*m*)	32.2	2.15 (*m*)	31.2	2.13 (*m*)	31.9	2.13 (*m*)
11	122.4	–	122.4	–	122.8	–	122.4	–
12	174.8	–	174.6	–	174.7	–	174.6	–
13	8.1	1.81 (*s*)	8.3	1.75 (*s*)	8.2	1.82 (*s*)	8.2	1.74 (*s*)
14	18.2	1.13 (*d*, J=7.4)	18.8	1.16 (*d*, J=7.2)	18.5	1.14 (*d*, J=7.4)	18.6	1.16 (*d*, J=7.2)
15	24.1	0.87 (*s*)	24.4	0.91 (*s*)	24.1	0.88 (*s*)	24.3	0.89 (*s*)
1′	167.3	–	167.5	–	166.8	–	176.3	–
2′	117.4	5.68 (*s*)	129.8	–	137.0	–	34.9	2.52 (*m*)
3′	157.2	–	137.3	6.85 (*q*, J=7.2)	125.4	6.10, 5.57 (2*s*)	19.4	1.15 (*d*, J=7.2)
4′	27.0	1.92 (*s*)	14.3	1.80 (*d*, J=7.2)	18.5	1.94 (*s*)	18.8	1.15 (*d*, J=7.2)
5′	20.4	2.18 (*s*)	12.2	1.84 (*s*)	–	–	–	–

Figure. *Conformation of eremophilanolides as a function of the configuration at C(8)*

Compound **4** was obtained in the form of colorless crystals. Its molecular formula was determined as $C_{19}H_{26}O_4$ by ESI-MS, the $[M+H]^+$ peak being observed at m/z 319.2. By NMR, the structure of **4** was determined as (8*R*)-2-[(methacroyl)oxy]eremophil-7(11)-en-12,8-olide. This is the first isolation of an eremophilanolide with a methacroyl (=2-methylprop-2-enoyl; Met) side chain, although neopetasol derivatives esterified with methacrylic acid were previously isolated from the rhizome extracts of *P. hybridus* [14].

Compound **5**, isolated as a mixture with **15**, was obtained as a yellowish, viscous mass. EI- and ESI-MS experiments indicated the molecular formula $C_{19}H_{28}O_4$. The

M^+ peak was detected at *m/z* 320.2 by ESI-MS. On the basis of NMR spectroscopic evidence, compound **5** was identified as (8*R*)-2-[(2-methylpropanoyl)oxy]eremophil-7(11)-en-12,8-olide. A neopetasol and an isopetasol derivative with isobutyric acid side chains were isolated before by *Neuenschwander et al.* [14] from *P. hybridus*, but no sesquiterpene lactones with this acid moiety have been reported from *P. hybridus*.

The new compound **8** was obtained together with the known compounds **6** and **7** in a ratio of 15 : 10 : 75 as a grayish-yellow, amorphous mass. The ^{1}H-NMR chemical shifts for H–C(3′), δ(H) 6.85 (*q*), were identical in **8** (*Table 2*) and in **3** (*Table 1*). In contrast to the structure elucidation described for **2**, the Me(15) group was shifted to lower field than that for Me(14). Therefore, the conformation of **8** was 'steroid-like', and the compound was identified as (8*S*)-2-[(tigloyl)oxy]eremophil-7(11)-en-12,8-olide.

Compound **9** was obtained as a grayish-yellow, amorphous substance. The molecular formula $C_{19}H_{26}O_4$ was deduced by EI-MS (*m/z* 232.2 ($[M-\text{MetOH}]^+$)) and ESI-MS (*m/z* 319.1 ($[M+\text{H}]^+$)). The most striking difference to **4** was the 'steroid-like' conformation indicated by the chemical shifts of Me(14) (δ(H) 0.85) and Me(15) (δ(H) 1.09). Therefore, **9** was identified as the 8β-epimer of **4**, *i.e.*, as (8*S*)-2-[(methacroyl)oxy]eremophil-7(11)-en-12,8-olide.

The molecular formula of the colorless, crystalline powder of **11** was $C_{20}H_{28}O_5$, as derived by EI-MS (*m/z* 348.1 (M^+)) and ESI-MS (*m/z* 349.1 ($[M+\text{H}]^+$). Again, the ^{1}H-NMR chemical shifts of Me(15) and Me(14) indicated a 'steroid-like' conformation, the side chain being identified as Ang. The major difference between **11** and all previous compounds was an OH group at C(9). Its equatorial orientation was derived from the large coupling constant (J = 11.4 Hz) between H–C(9) and H–C(8), which required a diaxial orientation of these H-atoms. Therefore, compound **11** was identified as (8*R*,9β)-2-[(angeloyl)oxy]-9-hydroxyeremophil-7(11)-en-12,8-olide, which is a new natural product.

Compound **12** had the molecular formula $C_{20}H_{28}O_6$ by ESI-MS (*m/z* 365.4 ($[M+\text{H}]^+$)). Comparison of the ^{1}H- and ^{13}C-NMR data of the side chain with those obtained for **11** revealed the presence of an Ang residue. Complete NMR assignment of **12** revealed that C(8) was quaternary (δ(C) 102.8), suggesting the presence of an additional OH group. By comparison of the ^{1}H-NMR shifts of Me(15) and Me(14) with those of other 8β congeners, the orientation of the 8-OH group was assumed as β. Therefore, compound **12** was identified as (8*R*,9β)-2-[(angeloyl)oxy]-8,9-dihydroxyeremophil-7(11)-en-12,8-olide. Like **11**, the higher-oxidized form **12** has never been isolated before.

Compound **15** formed a yellowish, viscous mass together with **5**. No parent peak for **15** was detected by EI- or ESI-MS. Complete NMR assignment (*Table 3*) revealed that **15** corresponds to 9-hydroxyisobakkenolide [10]. This structure was supported by EI-MS, with fragments at *m/z* 248.1 ($[M-\text{AngOH}]^+$) and 230.1 ($[M-\text{AngOH}-\text{H}_2\text{O}]^+$). Detailed analysis of the further fragmentation of these ions, which are characteristic for bakkenolides, have been described before [15]. Unlike known bakkenolides, compound **15** is the first representative of a bakkenolide-like compound with a C=C bond inside the γ-lactone ring: all other reported bakkenolides have an exocyclic C=C bond. The relative configuration of **15** at C(7) was determined by selective transient-NOE experiments. Inversion of H–C(9) led to NOEs at Me(13) and H_α–C(6) (δ(H) = 1.96). Inversion of Me(14) led to NOEs at H–C(10) and H_β–C(6)

Table 2. *^{1}H- and ^{13}C-NMR Data of* **8**, **9**, **11**, *and* **12**. At 600/150 MHz, resp. in $CDCl_3$ at 25°; δ in ppm, J in Hz. Asterisks (*) indicate interchangeable assignments.

Position	**8**		**9**		**11**		**12**	
	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)
1	32.1	1.79, 1.92 (2*m*)	32.3	1.76, 1.91 (2*m*)	26.3	1.72 (*td*, *J*=12.8, 4.7), 2.42 (*m*)	26.8	1.71 (*td*, *J*=12.8, 4.7), 2.31 (*dd*, *J*=12.8, 2.2)
2	68.6	4.95 (*m*)	69.4	4.91 (*m*)	68.3	4.95 (*m*)	68.3	4.92 (*m*)
3	35.9	1.37 (*q*, *J*=12.3), 1.87 (*m*)	35.8	1.35 (*q*, *J*=12.7), 1.88 (*m*)	36.0	1.43 (*q*, *J*=12.7), 1.91 (*m*)	35.7	1.43 (*q*, *J*=12.4), 1.88 (br. *s*)
4	29.5	1.65 (*m*)	29.6	1.62 (*m*)	31.2	1.47 (*m*)	31.0	1.49 (*m*)
5	39.2	–	39.3	–	40.7	–	39.4	–
6	35.6	1.94, 2.92 (2*d*, *J*=14.1 each)	35.8	2.89 (*d*, *J*=14.2), 1.92 (*m*)	36.06	2.01, 2.90 (2*d*, *J*=14.1 each)	33.6	2.21, 2.77 (2*d*, *J*=13.6 each)
7	160.0	–	160.3	–	156.0	–	154.8	–
8	79.9	4.62 (*dd*, *J*=11.4, 7.0)	80.0	4.6 (*m*)	86.1	4.48 (*d*, *J*=9.4)	102.8	–
9	35.7	1.68 (*q*, *J*=12.4), 2.29 (*ddd*, *J*=12.4, 6.7, 3.7)	36.0	1.65 (*q*, *J*=12.7), 2.28 (*m*)	73.7	3.88 (*ddd*, *J*=9.7, 8.3, 3.9)	73.1	3.88 (*d*, *J*=11.3)
10	40.9	1.87 (*m*)	41.3	1.87 (*m*)	47.4	1.77 (*ddd*, *J*=9.3, 4.6, 2.6)	46.6	1.79 (*td*, *J*=3.0, 11.6)
11	121.2	–	121.6	–	122.7	–	125.7	–
12	174.6	–	174.8	–	174.0	–	171.7	–
13	8.3	1.82 (*s*)	8.7	1.82 (*s*)	8.0	1.83 (*s*)	8.6	1.85 (*s*)
14	15.9	0.87 (*d*, *J*=6.7)	15.9	0.85 (*d*, *J*=6.8)	15.6	0.87 (*d*, *J*=6.7)	n.d.[a])	0.88 (*d*, *J*=6.2)
15	21.7	1.10 (*s*)	21.9	1.09 (*s*)	22.0	1.13 (*s*)	21.5	1.13 (*s*)
1′	167.5	–	167.3	–	167.4	–	167.5	–
2′	128.2	–	137.0	–	128.0	–	n.d.	–
3′	137.2	6.02 (*q*, *J*=7.3)	125.4	6.05, 5.52 (2*s*)	137.7	6.03 (*q*, *J*=7.3)	137.7	6.05 (*q*, *J*=7.3)
4′	15.7	1.95 (*d*, *J*=7.1)	18.6	1.91 (*s*)	16.0	1.96 (*d*, *J*=7.3)	15.9	1.95 (*d*, *J*=7.3)
5′	20.6	1.85 (br. *s*)	–	–	20.6	1.86 (*s*)	20.6	1.87 (*s*)

[a]) Not detected.

Table 3. *^{1}H- and ^{13}C-NMR Data of* **15** *and* **17**. At 600/150 MHz, resp., in (D_6)acetone (**15**) or $CDCl_3$ (**17**) at 25°; δ in ppm, J in Hz.

Position	**15**		**17**	
	δ(C)	δ(H)	δ(C)	δ(H)
1	27.9	1.66, 2.13 (2*m*)	27.8	2.60, 1.76 (2*m*)
2	69.9	5.01 (*m*)	68.9	4.79 (*m*)
3	37.3	1.39, 1.81 (2*m*)	35.5	1.43 (*q*, *J* = 12.0), 1.92 (*m*)
4	37.4	1.66 (*m*)	31.6	1.83 (*m*)
5	39.6	–	41.3	–
6	42.8	1.70 (*d*, *J* = 14.4), 1.96 (*m*)	31.5	2.43 (*d*, *J* = 17.4), 2.87 (*d*, *J* = 17.4)
7	59.4	–	136.7	–
8	181.7	–	146.5	–
9	76.3	4.36 (*d*, *J* = 12.0)	185.8	–
10	50.6	2.59 (*ddd*, *J* = 12.0, 6.0, 2.0)	54.0	2.61 (*m*)
11	121.2	–	121.1	–
12	137.2	6.76 (*s*)	145.1	7.40 (*s*)
13	8.1	1.77 (*s*)	8.1	2.00 (*s*)
14	16.4	0.92 (*d*, *J* = 6.6)	17.0	0.86 (*d*, *J* = 6.6)
15	20.5	1.10 (*s*)	22.8	1.18 (*s*)
1′	167.6	–	n.d.[a])	–
2′	129.3	–	116.7	5.63 (*s*)
3′	137.4	6.06 (*q*, *J* = 7.2)	156.5	–
4′	n.d.	1.94 (*d*, *J* = 7.3)	27.8	2.16 (*s*)
5′	20.5	1.85 (*s*)	20.8	1.88 (*s*)

[a]) Not detected.

(δ(H) = 1.70). This indicated α-orientation of H–C(9) and Me(13). Thus, compound **15** was identified as (3*R**,3′*R**,3a′*S**,5′*R**,7′*S**,7a′*R**)-1′,3′,3a′,4′,5′,6′,7′,7a′-octahydro-3′-hydroxy-4,7′,7a′-trimethyl-2-oxospiro[furan-3,2′-inden]-5′-yl (2*Z*)-2-methylbut-2-enoate.

Compound **16**, a colorless, amorphous powder, showed an ESI-MS peak at *m*/*z* 331.2 ($[M+H]^+$), in accord with the molecular formula $C_{20}H_{24}O_4$. The NMR data were in very good agreement with data published for 9-oxofuranopetasin [10]. Whereas **16** had been isolated by *Novotný et al.* [8] from the buds, and by *Siegenthaler* and *Neuenschwander* [16] from leaves and buds of *P. hybridus*, this is the first report of this compound from the *rhizomes* of this plant.

The ESI mass spectrum of **17**, obtained as a colorless, amorphous compound, exhibited the $[M+H]^+$ peak at *m*/*z* 331.1, consistent with the molecular formula $C_{20}H_{26}O_4$. The new compound **17** had the same furanoeremophilane skeleton as **16**, but the Ang residue of the latter was replaced by a Sen moiety in **17**. Therefore, its structure was assigned as 8,12-epoxy-2-[(senecioyl)oxy]eremophil-7,11-dien-9-one.

Compound **18** was obtained as colorless crystals. The molecular formula $C_{15}H_{20}O_3$ was deduced by EI- and ESI-MS experiments. The former revealed the M^+ peak at *m*/*z* 248.1 and the $[M - H_2O]^+$ signal at *m*/*z* 230.1. ESI-MS showed the $[M+H]^+$ signal at *m*/*z* 249.1, with a pronounced peak at *m*/*z* 231.1 due to loss of H_2O. The NMR data of **18** were in perfect agreement with the data published by *Zhao et al.* [17] for tsoongia-

nolide B. Until now, there has been no report on the isolation of this compound from *Petasites* plants. During NMR measurements, we observed that **18** was dehydrated to **19**, as observed before [17], leading to an additional C=C bond between C(1) and C(10). The resulting product **19** could be readily assigned as ligularenolide [18].

The first isolation of sesquiterpene esters with a furanoeremophilane skeleton as well as eremophilane lactones from *P. hybridus* was reported back in 1961 [19]. Eremophilanolides are considered to be the autoxidation products of furanoeremophilanes [20]. *Naya et al.* [11] transformed the furan petasalbin to the corresponding lactone by photosensitized oxygenation, and *Siegenthaler* and *Neuenschwander* [21] proposed a detailed reaction mechanism for acid-catalyzed conversion of 9-hydroxyfuranoeremophilanes to eremophilane lactones. The same authors assume that eremophilane lactones are secondary products arising from the corresponding 9-hydroxyfuranoeremophilanes during drying of the fresh plant or during storage [21]. Bakkenolides, which are related to 9-hydroxyisobakkenolide, are thought to be derivatives of eremophilanolides [22] or furanoeremophilanes, respectively [8].

We wish to thank *Weber & Weber*, Inning, Germany, for providing the *Petasites hybridus* extract and for recording mass spectra. Ing. *Elke Prettner* is acknowledged for carrying out the polarimetry experiments.

Experimental Part

1. *General.* Abbreviations: Ang, angeloyl; Sen, senecioyl; Tig, tigloyl; Met = methacroyl. Vacuum liquid chromatography (VLC): silica gel *60* (70–230 mesh; *Merck*). Column chromatography (CC): silica gel *60* (230–400 mesh; *Merck*). Anal. TLC: silica gel *60* F_{254} plates (*Merck*), eluting with toluene/AcOEt 80:20, visualization by spraying with 'anisaldehyde/H_2SO_4' reagent (anisaldehyde/AcOH/MeOH/H_2SO_4 0.5:10:85:5), followed by heating at 160° for 90 s and detection under UV/VIS light at 254 and 365 nm. Anal. HPLC: *Merck-Hitachi* system with *L-7100* pump, *L-7200* autosampler, UV/VIS *L-7455* diode-array detector (DAD), *D-7000 Chromatography Data Station Software HPLC System Manager* (Version 4.1), *Jetstream 2 Plus* (Ser. No. 120541) column thermostat, *LiChroCART RP-18* column (*LiChrospher-100*, 5 μm, 4×125 mm; *Merck*), flow 1 ml/min, column temp. 40°, UV detection at 230 nm, eluents: H_2O (*A*)/MeCN (*B*) gradient: 62–40% *A* in 18 min, 10 min at 40% *A*, 40–62% *A* in 2 min, with equilibration for 10 min. Semi-prep. HPLC: *Merck-Hitachi system*, with *L-6200-A Intelligent* pump, *L-4500* DAD, *Jetstream 2* (Ser. No. 60888 (0–80)) column thermostat, *D-6500 Chromatography Data Station Software DAD System Manager*, *LiChroCART RP*-18 column (*LiChrospher-100*, 10 μm, 10×250 mm; *Merck*), column temp. 40°, H_2O/MeCN gradient at 1.5–2 ml/min. Prep. HPLC: *Dynamax UV-1* detector (*Rainin*), *Dynamax SD-1* solvent-delivery system (*Rainin*), *Star Chromatography Workstation* (Version 5.31), all *Varian Associates*, *Hibar RP-18* column (*LiChrospher-100*, 10 μm, 25×250 mm; *Merck*), isocratic H_2O/MeCN 44:56, fixed wavelength 230 nm, eluent flow 30 ml/min at r.t. UV Spectra were recorded during HPLC with a DAD (see above); λ_{max} in nm (retention times t_R in min). Polarimetry: *Perkin-Elmer 241-MC* polarimeter, in 10-cm microcuvette. ^{1}H-, ^{13}C-, and 2D-NMR (HSQC, HMBC, DQF-COSY, NOESY) Experiments were performed with *Varian Unity-Inova-400* and *-600* spectrometers; δ in ppm rel. to Me_4Si, *J* in Hz; exper. parameters according to the literature [23]. Mass spectra: GC/MS: EI mode at 70 eV, scan range *m*/*z* 40–1000, *HP-5890 Series-II-plus* GC apparatus connected with a mass-selective *HP-5989B* detector, *HP Chemstation* software, He as carrier gas, *HP-5 MS* column (30 m, cross-linked with 5% PH-ME siloxane; i.d. 0.25 mm, film thickness 0.5 μm), injection and detection temp. 260 and 300°, resp., gradient mode: 150–280° at 8°/min, then 24 min isothermal. HPLC-DAD/ESI-MS (pos.): scan range *m*/*z* 50–1000, HPLC mode: see anal. HPLC; on a *Thermo Finnigan Surveyor* liquid chromatograph, with *Thermo Quest Surveyor* PDA detector, *Thermo Finnigan Surveyor* autosampler, *Thermo Quest Surveyor* MS pump, *Thermo Finnigan LCQ-Deca-XP* mass detector.

2. *Plant Material*. A commercial, solvent-free supercritical-CO_2 'spissum' extract of butterbur rhizomes was supplied by *Weber & Weber*, Inning, Germany. The content of petasins was labeled 2.6%. The extract was described as being rich in furanoeremophilanes. The drug-to-extract ratio was 28:1 to 44:1.

3. *Extraction and Isolation*. The solvent-free CO_2 'spissum' extract of the rhizomes of *P. hybridus* (12 g; *Weber & Weber*) was separated by VLC (SiO_2; hexane/AcOEt/MeOH gradient) to afford five fractions, *Fr. I–V*. *Fr. III* and *IV* were combined and further fractionated to provide 16 sub-fractions, *Fr. A–P*, by CC (SiO_2; hexane/AcOEt/MeOH gradient). All sub-fractions were allowed to crystallize. The crystallization solvent was AcOEt for *Fr. B*, *D–F*, *I*, *J*, and *L*. The purity of the isolated products was confirmed by ^{1}H-NMR experiments. Further trials for a better separation of several compound mixtures and purification of most of the isolation products were limited by the low sample amounts. Crystals obtained from *Fr. B* were further purified by CC (SiO_2; hexane/AcOEt gradient) to afford **14** (purity 80%). The mother liquor of *Fr. D* was subjected to prep. HPLC to afford **21** (purity 50%), **20** (purity $\geq$93%), **6** (purity 93%), and a mixture of **16**/**17**, which was separated by semi-prep. HPLC to afford **16** (purity 85%) and **17** (purity 80–85%). Prep. HPLC of the crystals obtained from *Fr. E* gave **6** (major peak; purity 95%) and **9** (minor peak; purity 97%). From the crystals of *Fr. F*, compounds **13** (purity $\geq$97%), **9** (purity 98%), a mixture of **7**/**6**/**8** 75:10:15, and a mixture of **6**/**8** 97:3 were obtained by prep. HPLC. By prep. HPLC of *Fr. G*, compound **1** (purity $\geq$99%) and a mixture of **13**/**18**/**4** (purity 90%) was obtained; compound **4** was further purified by semi-prep. HPLC to 97% purity. After semi-prep. HPLC of the remaining mixture of **13**/**18**, the purity of individual **13** was 99%. A few weeks after the first NMR experiments, new 1D- and 2D-NMR spectra were recorded with the original samples kept in $CDCl_3$ soln. These experiments revealed that **18** had been transformed into **19** in the meantime. Semi-prep. HPLC of *Fr. H* gave **3** (purity 75%), a mixture of **1**/**2** 10:3, **4** (purity 99%), a mixture of at least two very polar, so far unknown 8α-H-eremophilanolides, and a mixture of **5**/**15**. Further separation of the unknown compounds and of **5**/**15** by semi-prep. HPLC were unsuccessful. Crystals from *Fr. I* and *Fr. J* gave **10**, with purities of 95% and $\geq$98%, resp. By semi-prep. HPLC, crystals of *Fr. L* could be separated into the main compound **11** (purity 99%) and a small amount of **12** (purity $\geq$97%).

4. *Compound Characterization. (8*R*)-2-[(Angeloyl)oxy]eremophil-7(11)-en-12,8-olide* (**1**). Colorless to pale-yellow amorphous powder. TLC: R_f 0.38 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: purple spot, at 366 nm light-blue fluorescence). HPLC-UV: 220.5 (t_R 18.61). ORD (MeOH, c = 0.57 mg/ml): $[\alpha]_{589}^{25} = -31.58$, $[\alpha]_{546}^{25} = -35.09$. ^{1}H- and ^{13}C-NMR: see [10]. GC/EI-MS: 332.2 (0.9, M^+), 281.0 (1.7), 267.2 (0.8), 253.1 (1), 234.1 (4), 232.2 (36, $[M-\text{AngOH}]^+$), 217.1 (10), 203.1 (4), 187.1 (11), 177.1 (6), 159.1 (14), 145.1 (5), 132.1 (10), 126.1 (25), 121.1 (45), 107.1 (28), 93.2 (25), 83.0 (79, $[M-249]^+$), 67.0 (13), 55.0 (100), 41.0 (44). HPLC-DAD/ESI-MS: 996.7 (1, $[3\,M+\text{H}]^+$), 937.3 (1), 852.5 (1), 790.7 (1), 704.4 (2, $[2\,M+\text{H}+\text{K}]^{2+}$), 665.0 (2, $[2\,M+\text{H}]^+$), 576.4 (1), 558.9 (4), 509.4 (1), 430.2 (2), 392.0 (4, $[M+\text{H}+\text{K}+\text{H}_2\text{O}]^{2+}$), 374.8 (11), 373.5 (100, $[M+\text{H}+\text{K}]^{2+}$), 334.2 (10, $[M+2\,\text{H}]^{2+}$), 333.2 (53, $[M+\text{H}]^+$), 274.1 (2), 233.2 (5, $[M+\text{H}-\text{AngOH}]^+$), 215.3 (1 $[M+\text{H}-\text{AngOH}-\text{H}_2\text{O}]^+$), 100.7 (3).

*(8*R*)-2-[(Senecioyl)oxy]eremophil-7(11)-en-12,8-olide* (**2**). Whitish, viscous mass, isolated together with **1**. TLC (single spot): R_f 0.39 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: purple spot, at 366 nm intensive light-blue fluorescence). HPLC-UV: no separation from **1**. ^{1}H- and ^{13}C-NMR: see *Table 1*. MS: no separation from **1**. GC/EI-MS (t_R 21.260): 355.0 (0.8, $[M+\text{Na}]^+$), (332.3 (1.4, M^+), 302.2 (0.9), 281.0 (3), 266.9 (0.9), 253.1 (2), 249.1 (1, $[M-83]^+$), 234.2 (7), 232.2 (55, $[M-100]^+$), 217.1 (18), 199.1 (7), 187.2 (19), 171.1 (8), 159.1 (20), 133.1 (13), 121.1 (67), 107.1 (41), 91.0 (28), 83.0 (100), 67.0 (17), 55.0 (97), 41.0 (48). HPLC-DAD/ESI-MS (t_R 13.96): 968.9 (1), 894.2 (1), 850.2 (2), 723.4 (1), 666.1 (4), 665.0 (10, $[2\,M+\text{H}]^+$), 576.0 (1), 558.7 (3), 532.2 (1), 392.9 (2), 391.8 (8, $[M+\text{H}+\text{K}+\text{H}_2\text{O}]^{2+}$), 374.8 (19), 373.7 (100, $[M+\text{H}+\text{K}]^{2+}$), 334.3 (15, $[M+2\,\text{H}]^{2+}$), 333.2 ($[M+\text{H}]^+$), 273.6 (2), 233.2 (7, $[M+\text{H}-\text{C}_5\text{H}_8\text{O}_2]^+$), 215.3 (1, $[M+\text{H}-\text{C}_5\text{H}_8\text{O}_2-\text{H}_2\text{O}]^+$), 163.2 (1), 100.8 (1).

*(8*R*)-2-[(Tigloyl)oxy]eremophil-7(11)-en-12,8-olide* (**3**). Whitish, viscous material. TLC: R_f 0.34 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: purple spot, at 366 nm light-blue fluorescence). HPLC-UV: 220.5 (t_R 17.47). ^{1}H- and ^{13}C-NMR: see *Table 1*. GC/EI-MS (t_R 22.413): 405.2 (0.4), 355.1 (0.5, $[M+\text{Na}]^+$), 332.2 (1.5, M^+), 327.1 (0.5), 302.3 (0.7), 281.8 (0.9), 281.1

(2), 253.1 (1), 249.2 (0.7, $[M-83]^+$), 232.2 (78, $[M-\text{TigOH}]^+$), 217.1 (26), 207.1 (9), 187.1 (20), 177.1 (8), 159.3 (24), 132.1 (15), 121.1 (85), 107.0 (37), 83.0 (99), 79.2 (20), 55.0 (100), 40.9 (30). HPLC-DAD/ESI-MS (t_R 13.01): 987.1 (1), 892.7 (1), 849.3 (1), 824.3 (1), 703.6 (3), 664.9 (5, $[2\,M+H]^+$), 558.8 (3), 508.6 (1), 393.1 (3), 391.9 (6, $[M+H+K+H_2O]^{2+}$), 374.8 (16), 373.6 (100, $[M+H+K]^{2+}$), 334.2 (12, $[M+2\,H]^{2+}$), 333.2 (71, $[M+H]^+$), 274.0 (2), 233.2 (7.5, $[M+H-\text{TigOH}]^+$), 215.3 (2, $[M+H-\text{TigOH}-H_2O]^+$), 100.7 (2).

*(8*R*)-2-[(Methacroyl)oxy]eremophil-7(11)-en-12,8-olide* (**4**). Small, colorless crystals. TLC: R_f 0.39 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: purple spot, at 366 nm reddish-purple fluorescence). HPLC-UV: 218.6 (t_R 15.20). ORD (MeOH; $c=0.79$ mg/ml): $[\alpha]_{589}^{27}=-26.58$, $[\alpha]_{546}^{27}=-31.65$. ^{1}H- and ^{13}C-NMR: see *Table 1*. GC/EI-MS: 341.1 (0.9, $[M+Na]^+$), 281.2 (2), 267.1 (1), 252.9 (1), 232.1 (48, $[M-\text{MetOH}]^+$), 217.1 (16), 208.0 (4), 186.4 (7), 171.1 (7), 159.1 (20), 145.1 (8), 132.1 (12), 121.1 (72), 107.1 (39), 93.0 (31), 79.0 (19), 69.0 (67), 53.0 (19), 41.0 (100). HPLC-DAD/ESI-MS: 976.5 (1), 855.2 (1), 815.0 (1), 717.1 (1), 676.2 (4), 637.0 (4, $[2\,M+H]^+$), 537.9 (3), 447.7 (2), 399.4 (3), 377.9 (5, $[M+H+K+H_2O]^{2+}$), 360.8 (14), 359.6 (100, $[M+H+K]^{2+}$), 320.2 (13, $[M+2\,H]^{2+}$), 319.2 (64, $[M+H]^+$), 273.9 (3), 233.2 (5, $[M+H-\text{TigOH}]^+$), 215.3 (1, $[M+H-\text{MetOH}-H_2O]^+$), 100.8 (2).

*(8*R*)-2-[(2-Methylpropanoyl)oxy]eremophil-7(11)-en-12,8-olide* (**5**). Yellowish, viscous mass, together with **15**. TLC: R_f *ca.* 0.35 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: purple spot, at 366 nm intensive light-blue fluorescence). HPLC-UV: 220.5 (t_R 15.79). ^{1}H- and ^{13}C-NMR: see *Table 1*. GC/EI-MS: 330.8 (0.2), 327.2 (0.2), 321.3 (1), 320.2 (1, M^+), 302.3 (0.2), 291.2 (0.6), 281.1 (0.7), 269.0 (0.2), 249.2 (0.7, $[M-71]^+$), 233.2 (25), 232.1 (69, $[M-C_4H_8O_2]^+$), 217.1 (30), 199.2 (10), 187.1 (29), 171.1 (10), 159.3 (29), 145.1 (8), 126.1 (53), 121.1 (100), 107.0 (48), 93.0 (31), 81.0 (20), 71.0 (26), 55.0 (22), 43.0 (93, $[M-277]^+$). HPLC-DAD/ESI-MS: 980.4 (1), 861.9 (1), 821.1 (2), 776.1 (1), 657.8 (3), 642.1 (30, $[2\,M+2\,H]^{2+}$), 641.1 (100, $[2\,M+H]^+$), 639.5 (4), 586.1 (1), 553.1 (1), 503.3 (1), 410.2 (1), 384.0 (4), 380.0 (7, $[M+H+K+H_2O]^{2+}$), 362.9 (13), 361.8 (73, $[M+H+K]^{2+}$), 337.7 (13), 322.5 (6, $[M+2\,H]^{2+}$), 321.4 (49, $[M+H]^+$), 303.6 (<5, $[M+H-H_2O]^+$), 273.9 (2), 233.3 (5, $[M+H-C_4H_8O_2]^+$), 215.3 (1, $[M+H-C_4H_8O_2-H_2O]^+$), 153.2 (1), 104.8 (1).

*(8*S*)-2-[(Angeloyl)oxy]eremophil-7(11)-en-12,8-olide* (**6**). Colorless to pale-yellow crystals, together with **8** (3%). TLC (single spot): R_f 0.44 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: purple spot, at 366 nm light-blue fluorescence). HPLC-UV (single peak with **8**): 220.5 (t_R 19.71). ORD (MeCN; $c=0.95$ mg/ml, 25°): positive signs at 589 and 546 nm. ^{1}H- and ^{13}C-NMR: see [10]. MS: no separation from **8**. GC/EI-MS: 355.2 (2, $[M+Na]^+$), 332.3 (5, M^+), 281.1 (5), 266.9 (54), 249.1 (3, $[M-83]^+$), 235.2 (2), 233.1 (100), 232.2 (30, $[M-100]^+$) 207.1 (18), 203.1 (7), 187.1 (15), 165.1 (17), 159.3 (13), 133.1 (11), 121.1 (37), 108.1 (33), 91.0 (25), 83.0 (79), 67.0 (18), 55.0 (89), 41.0 (78). HPLC/ESI-MS: 955.6 (1), 853.2 (1), 850.5 (4), 825.0 (1), 704.4 (4), 666.2 (9), 665.1 (18, $[2\,M+H]^+$, 663.3 (1), 559.5 (2), 530.4 (2), 393.1 (2), 392.0 (5, $[M+H+K+H_2O]^{2+}$), 374.7 (17), 373.5 (100, $[M+H+K]^{2+}$), 334.1 (9 $[M+2\,H]^{2+}$), 333.1 (39, $[M+H]^+$), 274.0 (3), 233.2 (10, $[M+H–100]^+$), 215.2 (1, $[M+H–100-H_2O]^+$), 100.8 (1).

*(8*S*)-2-[(Senecioyl)oxy]eremophil-7(11)-en-12,8-olide* (**7**). Grey-to-yellow, amorphous material, together with **6** (10%) and **8** (15%). TLC (one spot together with **6** and **8**): R_f 0.44 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: purple spot, at 366 nm light-blue fluorescence). HPLC-UV (one peak with **6** and **8**): 220.5 (t_R 19.09). ^{1}H- and ^{13}C-NMR: see [10]. MS: no separation from **8**. GC/EI-MS (t_R 22.001): 332.2 (1, M^+), 281.1 (0.8), 249.2 (3, $[M-83]^+$), 234.2 (4), 232.1 (33, $[M-100]^+$), 217.2 (5), 203.1 (4), 187.1 (6), 177.3 (3), 165.1 (8), 145.1 (4), 126.1 (14), 121.1 (18), 107.0 (18), 86.0 (16), 83.0 (100), 67.0 (9), 55.0 (36), 41.0 (46). HPLC-DAD/ESI-MS (t_R 14.47): 947.4 (1), 850.4 (4), 782.0 (1), 704.1 (2), 667.1 (21), 665.1 (54, $[2\,M+H]^+$), 663.3 (1), 558.5 (1), 530.7 (1), 393.1 (2), 392.0 (8, $[M+H+K+H_2O]^{2+}$), 374.9 (16), 373.7 (100, $[M+H+K]^{2+}$), 334.3 (8, $[M+2\,H]^{2+}$), 333.3 (44, $[M+H]^+$), 273.9 (5), 233.3 (13, $[M+H–100]^+$), 215.3 (2, $[M+H-100-H_2O]^+$), 100.9 (1).

*(8*S*)-2-[(Tigloyl)oxy]eremophil-7(11)-en-12,8-olide* (**8**). For appearance, TLC, UV, and MS, see data of **6** and **7**. ^{1}H- and ^{13}C-NMR: see *Table 2*.

*(8*S*)-2-[(Methacroyl)oxy]eremophil-7(11)-en-12,8-olide* (**9**). Grey-to-yellow, amorphous material. TLC: R_f 0.47 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: purple spot, at 366 nm blue fluorescence). HPLC-UV: 216.6 (t_R 16.72). ORD (MeOH; $c=0.865$ mg/ml):

$[\alpha]_{589}^{23} = +10.40$, $[\alpha]_{546}^{23} = +15.03$. ^{1}H- and ^{13}C-NMR: see *Table 2*. GC/EI-MS: 289.2 (2), 281.1 (2), 249.1 (1, $[M-69]^+$), 232.2 (46, $[M-\text{MetOH}]^+$), 228.6 (0.6), 217.2 (11), 203.2 (6), 187.2 (10), 176.3 (5), 165.1 (10), 159.1 (14), 147.1 (7), 126.1 (31), 121.1 (51), 108.0 (46), 93.0 (26), 79.0 (20), 69.0 (77), 55.0 (21), 43.0 (18), 41.0 (100). HPLC-DAD/ESI-MS: 971.4 (1), 931.2 (1), 818.2 (1), 815.4 (5), 719.0 (1), 676.7 (2, $[2M+H+K]^{2+}$), 638.1 (8), 637.0 (19, $[2M+H]^+$), 587.1 (1), 537.8 (2), 509.9 (1), 379.0 (3), 377.9 (7, $[M+H+K+H_2O]^{2+}$), 364.5 (<5, $[M+2\,Na]^{2+}$), 360.6 (19), 359.5 (100, $[M+H+K]^{2+}$), 320.2 (8 $[M+2\,H]^{2+}$), 319.1 (46, $[M+H]^+$), 274.0 (3), 233.2 (10, $[M+H-\text{MetOH}]^+$), 215.1 (2, $[M+H-\text{MetOH}-H_2O]^+$), 100.6 (1).

*(8*S*)-2-{[(*Z*)-3-(Methylsulfanyl)prop-2-enoyl]oxy}eremophil-7(11)-en-12,8-olide* (**10**). Thin, colorless needles or light-yellow crystal powder. TLC: R_f 0.40 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: faint-purple spot, at 366 nm weak-blue fluorescence). HPLC-UV: 220.5, 288.1 (t_R 14.37). ORD (MeOH; $c = 0.54$ mg/ml): $[\alpha]_{589}^{25} = -18.52$, $[\alpha]_{546}^{25} = -24.07$. ^{1}H- and ^{13}C-NMR: see [10]. GC/EI-MS: 351.1 (2), 350.2 (9, M^+), 281.0 (2), 249.2 (4, $[M-101]^+$), 234.1 (13), 233.1 (62), 232.2 (21, $[M-C_4H_6O_2S]^+$), 231.1 (7), 215.1 (8), 207.0 (13), 191.0 (8), 187.1 (8), 165.1 (10), 151.1 (5), 147.1 (8), 133.1 (10), 126.1 (11), 121.1 (23), 120.1 (12), 119.0 (30), 118.1 (41), 110.0 (8), 109.1 (13), 108.1 (22), 107.1 (26), 106.1 (8), 103.0 (25), 101.0 (100), 93.2 (22), 91.0 (22), 79.0 (21), 73.9 (32), 73.0 (26), 55.0 (23), 41.0 (35). HPLC-DAD/ESI-MS: 957.2 (1), 903.2 (3), 896.9 (6), 895.4 (14), 888.1 (7), 881.3 (2), 750.6 (1), 704.1 (3), 702.1 (26), 701.1 (76, $[2M+H]^+$), 700.2 (1), 587.0 (1), 565.2 (5), 511.2 (1), 412.1 (2), 410.0 (10, $[M+H+K+H_2O]^{2+}$), 392.9 (17), 391.8 (100, $[M+H+K]^{2+}$), 368.2 (3, $[M+H_2O]^+$), 355.1 (<5, $[M+Na-H_2O]^+$), 352.2 (10, $[M+2\,H]^{2+}$), 351.1 (49, $[M+H]^+$), 274.9 (1), 274.0 (7), 233.3 (22, $[M+H-C_4H_6O_2S]^+$), 118.9 (1, $C_4H_7O_2S^+$), 100.9 (2).

*(8*R*,9β)-2-[(Angeloyl)oxy]-9-hydroxyeremophil-7(11)-en-12,8-olide* (**11**). Colorless, crystalline powder. TLC: R_f 0.15 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: faint purple spot, at 366 nm blue fluorescence). HPLC-UV: 220.5 (t_R 12.37). ORD (MeOH; $c = 0.63$ mg/ml): $[\alpha]_{589}^{28} = -17.46$; $[\alpha]_{546}^{28} = -20.63$. ^{1}H- and ^{13}C-NMR: see *Table 2*. GC/EI-MS: 429.1 (1), 355.2 (2), 348.1 (2, M^+), 327 (2), 281,1 (6), 265.2 (3, $[M-83]^+$), 249.2 (49), 248.2 (18, $[M-\text{AngOH}]^+$), 231,2 (21), 230.1 (21), 219.1 (13), 215.1 (13), 207.1 (25), 192.1 (4), 191.1 (8), 189.1 (6), 175.1 (12), 173.1 (9), 163.1 (13), 137.1 (20), 119.0 (22), 109.1 (55), 107.1 (38), 100.1 (15), 93.0 (19), 91.0 (21), 83.0 (69, $[M-265]^+$), 67.0 (22), 55 (100), 43.0 (36), 41.0 (51). HPLC-DAD/ESI-MS: 948.9 (2), 891.9 (4), 890.9 (8), 883.0 (4), 777.0 (5), 719.2 (1, $[2M+Na]^+$), 699.2 (12), 698.3 (35), 697.3 (100, $[2M+H]^+$), 679.5 (1), 568.7 (1), 542.6 (3), 413.1 (2), 408.0 (2, $[M+H+K+H_2O]^{2+}$), 391.1 (4), 389.9 (21, $[M+H+K]^{2+}$), 349.1 (12, $[M+H]^+$), 289.9 (5), 249.1 (8, $[M-\text{AngOH}]^+$), 231.1 (2, $[M+H-\text{AngOH}-H_2O]^+$), 175.3 (1), 100.6 (1).

*(8*R*,9β)-2-[(Angeloyl)oxy]-8,9-dihydroxyeremophil-7(11)-en-12,8-olide* (**12**). Colorless, amorphous, partly viscous material. TLC: R_f 0.14 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: purple spot, at 366 nm intensive-blue fluorescence). HPLC-UV: 220.5 (t_R 10.61). ^{1}H- and ^{13}C-NMR: see *Table 2*. GC/EI-MS: neither the M^+ nor the $[M-\text{AngOH}]^+$ peaks were detectable, probably due to decomposition or bad GC mobility; scan at t_R 15.755: α-splitting at m/z 83 indicated the presence of **12** (or a compound with the same acid residue); further fragments: 281 (6, $[M-83]^+$), 220 (100, $[M-\text{AngOH}-CO_2]^+$). HPLC-DAD/ESI-MS: 954.2 (1), 930.2 (3), 835.9 (2), 809.0 (4), 752.2 (10), 751.2 (32, $[2M+Na]^+$), 746.3 (48), 729.5 (100, $[2M+H]^+$), 712.4 (3), 598.9 (1), 567.4 (1), 528.9 (1), 428.0 (4), 406.0 (5, $[M+H+H_2O+Na]^{2+}$), 382.7 (3, $[M+H+H_2O]^+$), 366.3 (2, $[M+2\,H]^{2+}$), 365.4 (5, $[M+H]^+$), 347.4 (5, $[M+H-H_2O]^+$), 265.3 (2, $[M+H-\text{AngOH}]^+$), 247.3 (5, $[M+H-\text{AngOH}-H_2O]^+$), 219.4 (1), 104.8 (1).

8β-Hydroxyeremophilanolide (*=(8*S*)-8-Hydroxyeremophil-7(11)-en-12,8-olide*; **13**). Small, colorless needles. TLC: R_f 0.30 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: very weak, purple spot, at 366 nm purple fluorescence). HPLC-UV: 222.6 (t_R 9.71). ORD (MeOH; $c = 0.51$ mg/ml): $[\alpha]_{589}^{25} = +50.98$, $[\alpha]_{546}^{25} = +60.78$. ^{1}H- and ^{13}C-NMR: see [10]. GC/EI-MS: 281.0 (72), 250.2 (3, M^+), 232.1 (8), 222.2 (29), 205.2 (6), 177.3 (4), 189.2 (6), 161.1 (8), 150.0 (7), 135.1 (6), 126.0 (16), 110.1 (11), 109.1 (100), 91.0 (15), 84.0 (18), 67.0 (22), 57.0 (22), 48.9 (32), 41.0 (44). HPLC-DAD/ESI-MS: 993.6 (1), 930.4 (1), 813.0 (1), 767.9 (9), 728.8 (2), 645.8 (1), 540.3 (4), 501.0 (4, $[2M+H]^+$), 435.8 (3), 351.6 (8), 292.8 (12), 291.8 (100, $[M+H+K]^{2+}$), 273.8 (33, $[M+Na]^+$), 252.1 (13, $[M+2\,H]^{2+}$), 251.1 (95, $[M+H]^+$), 233.2 (45, $[M+H-H_2O]^+$), 221.2 (6), 207.4 (2), 104.9 (3), 100.7 (7), 93.1 (1).

8β-H-Eremophilanolide (=*(8*S*)-Eremophil-7(11)-en-12,8-olide*; **14**). Small, colorless crystals. TLC: R_f 0.38 (before spraying: no fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: weak-purple spot, at 366 nm weak grey-to-red fluorescence). HPLC-UV: 222.6 (t_R 16.24). ORD (MeOH; $c=0.54$ mg/ml): $[\alpha]_{589}^{28}=+35.19$; $[\alpha]_{546}^{28}=+42.59$. ^{1}H- and ^{13}C-NMR: see [10]. GC/EI-MS: 234.2 (5, M^+), 219.1 (1), 216.2 (0.9), 207.0 (2), 189.2 (3), 187.1 (0.9), 173.1 (2), 161.1 (4), 147.1 (7), 135.1 (5), 125.1 (31), 124.3 (16), 123.1 (100), 121.1 (9), 112.1 (27), 110.0 (37), 109.1 (25), 108.1 (17), 107.1 (12), 105.0 (10), 95.2 (13), 93.2 (17), 91.0 (19), 85.9 (14), 84.0 (20), 82.0 (17), 81.0 (32), 79.0 (18), 77.0 (14), 67.0 (27), 57.0 (23), 56.0 (12), 55.0 (28), 53.0 (25), 51.0 (16), 48.9 (33), 43.0 (28), 42.0 (16), 40.9 (61). HPLC-DAD/ESI-MS: 984.5 (1), 870.4 (1), 818.8 (1), 781.1 (1), 684.2 (1), 613.7 (1), 544.4 (1), 470.0 (2, $[2\,M+2\,H]^{2+}$), 469.0 (6, $[2\,M+H]^+$), 411.8 (2), 383.6 (1), 293.9 (8, $[M+H+K+H_2O]^{2+}$), 276.8 (13), 275.6 (100, $[M+H+K]^{2+}$), 236.2 (10, $[M+2\,H]^{2+}$), 235.2 (75, $[M+H]^+$), 153.1 (2), 100.9 (1).

9-Hydroxyisobakkenolide (=*(3*R**,3′*R**,3a′*S**,5′*R**,7′*S**,7a′*R**)-1′,3′,3a′,4′,5′,6′,7′,7a′-Octahydro-3′-hydroxy-4,7′,7a′-trimethyl-2-oxospiro[furan-3,2′-inden]-5′-yl (2*Z*)-2-Methylbut-2-enoate*; **15**). Yellowish, viscous mass, together with **5**. TLC: R_f 0.26 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: intensive reddish-purple spot, at 366 nm almost black fluorescence). HPLC-UV: 218.6 (t_R 16.98). ^{1}H- and ^{13}C-NMR: see *Table 3*. GC/EI-MS: 355.2 (1), 348 (M^+, $C_{20}H_{28}O_5^+$) not obs., 281.1 (2), 267.1 (1), 249.2 (8), 248.1 (41), 230.1 (4), 207.1 (10), 202.2 (12), 187.2 (4), 163.3 (4), 149.0 (5), 138.1 (100), 120.0 (27), 109.0 (84), 93.0 (18), 83.0 (36), 67.0 (20), 55.0 (72), 41.0 (34). HPLC-DAD/ESI-MS (pos.): not assignable.

9-Oxofuranopetasin (=*2-[(Angeloyl)oxy]-8,12-epoxyeremophil-7,11-dien-9-one*; **16**). Colorless, amorphous material. TLC: R_f 0.49 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: intensive-purple spot, at 366 nm deep-blue fluorescence). HPLC-UV: 216.6 , 282.7 (t_R 21.41). ^{1}H- and ^{13}C-NMR: see [10]. HPLC-DAD/ESI-MS: 993.3 (1), 927.8 (1), 834.1 (1), 745.3 (1), 685.1 (1), 683.0 (10), 660.9 (17, $[2\,M+H]^+$), 636.5 (1), 560.9 (1), 516.0 (1), 414.2 (1), 393.7 (5), 389.8 (9), 349.0 (14, $[M+H+H_2O]^+$), 348.0 (66), 332.2 (19, $[M+2\,H]^{2+}$), 331.2 (100, $[M+H]^+$), 249.1 (1), 232.3 (4), 231.3 (21, $[M+H-AngOH]^+$), 203.3 (1), 161.2 (5), 105.0 (1).

8,12-Epoxy-2-[(senecioyl)oxy]eremophil-7,11-dien-9-one (**17**). Colorless, amorphous material. TLC: R_f 0.48 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: intensive purple spot, at 366 nm deep-blue fluorescence). HPLC-UV: 218.6, 282.7 (t_R 20.83). ^{1}H- and ^{13}C-NMR: see *Table 3*. HPLC-DAD/ESI-MS: 967.4 (1), 938.5 (1), 831.2 (1), 744.8 (1), 685.0 (1), 683.1 (13), 662.0 (1), 660.9 (16, $[2\,M+H]^+$), 660.1 (1), 561.0 (1), 507.8 (1), 394.6 (2), 393.4 (7), 349.1 (10, $[M+H+H_2O]^+$), 348.0 (52), 332.2 (23, $[M+2\,H]^{2+}$), 331.1 (100, $[M+H]^+$), 249.2 (1), 232.4 (4), 231.3 (25, $[M+H-SenOH]^+$), 213.2 (2), 161.2 (5), 135.2 (1), 91.0 (1).

Tsoongianolide B (=*(10β)-10-Hydroxyeremophil-7(11),8-dien-12,8-olide*; **18**). Colorless crystals. TLC: R_f 0.27 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: very weak purple spot; at 366 nm intensive blue fluorescence). HPLC-UV: 273.3 (t_R 8.29). ^{1}H- and ^{13}C-NMR: see [17]. GC/EI-MS: 248.1 (4, M^+), 230.1 (10), 219.2 (4), 215.1 (6), 207.0 (7), 189.2 (4), 187.2 (8), 178.0 (22), 177.1 (23), 163.1 (14), 160.1 (14), 150.1 (19), 149.1 (8), 131.1 (6), 125.1 (29), 115.1 (8), 107.1 (13), 91.2 (19), 86.0 (40), 83.9 (51), 77.0 (17), 69.0 (20), 57.0 (53), 56.2 (35), 55.0 (24), 53.0 (19), 51.0 (40), 49.0 (100), 46.9 (20), 44.0 (13), 43.0 (80), 41.9 (34), 41.0 (91). HPLC-DAD/ESI-MS: 998.3 (1), 942.0 (1), 837.3 (1), 795.4 (1), 707.4 (1), 669.3 (1), 587.1 (1), 510.4 (1), 460.7 (2), 350.0 (1), 291.7 (3), 289.6 (93, $[M+H+K]^{2+}$), 271.8 (5, $[M+Na]^+$), 250.1 (18, $[M+2\,H]^{2+}$), 249.1 (100, $[M+H]^+$), 231.2 (38, $[M+H-H_2O]^+$), 175.2 (2), 104.7 (1).

Ligularenolide (=*Eremophil-1(10),7(11),8-trien-12,8-olide*; **19**). Main dehydration product of **18**. TLC (main spot): R_f 0.76 (before spraying: fluorescence quenching at 254 nm, very intensive light-blue fluorescence at 366 nm; anisaldehyde/H_2SO_4: very weak red spot, intensive-blue fluorescence at 366 nm). HPLC-UV: no assignment possible. ^{1}H- and ^{13}C-NMR: see [18]. HPLC-DAD/ESI-MS: 995.3 (1), 915.2 (1), 877.9 (1), 821.5 (1), 757.3 (1), 665.1 (1), 604.3 (1), 558.3 (1), 460.7 (1, $[2\,M+H]^+$), 391.1 (2), 311.0 (1), 272.8 (5), 271.7 (39, $[M+H+K]^{2+}$), 232.3 (14, $[M+2\,H]^{2+}$), 231.2 (100, $[M+H]^+$), 216.2 (2), 104.9 (1), 100.8 (4).

Iso-S-petasin (=*8-Oxoeremophil-7(11),9-dien-3-yl (*Z*)-3-(Methylsulfanyl)prop-2-enoate*; **20**). Transparent, viscous and white, amorphous appearance. TLC: R_f 0.49 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: brown spot, at 366 nm intensive white-blue fluorescence). HPLC-

UV: 248.0, 288.1 (t_R 16.77). ORD (MeOH; $c = 1.64$ mg/ml): $[\alpha]_{589}^{25} = +9.15$, $[\alpha]_{546}^{25} = +4.88$. ^{1}H- and ^{13}C-NMR: see [24]. GC/EI-MS: 334.2 (10, M^+), 281.1 (0.3), 253.1 (0.1), 233.2 (0.6), 216.1 (98, $[M - C_5H_8OS]^+$), 201.2 (33), 187.1 (8), 173.1 (14), 161.1 (100), 160.1 (32), 147.1 (13), 133.1 (13), 119.1 (9), 105.1 (12), 101.0 (25), 91.0 (12), 73.0 (7), 67.0 (4), 57.0 (6), 41.0 (18). HPLC-DAD/ESI-MS: 970.3 (1), 936.8 (1), 832.5 (1), 705.7 (1), 668.5 (1), 556.2 (1), 520.9 (1), 455.4 (1), 375.0 (2, $[M + H + K]^{2+}$), 337.0 (8), 336.0 (25, $[M + 2\,H]^{2+}$), 335.0 (100, $[M + H]^+$), 332.9 (1), 218.2 (2), 217.3 (7, $[M + H - C_5H_8OS]^+$), 147.1 (2), 100.8 (1).

Neo-S-petasin (=*8-Oxoeremophil-9,11-dien-3-yl (Z)-3-(Methylsulfanyl)prop-2-enoate*; **21**). Colorless crystals mixed with transparent, viscous parts. TLC: R_f 0.50 (before spraying: fluorescence quenching at 254 nm; anisaldehyde/H_2SO_4: brown spot, at 366 nm intensive white-blue fluorescence). HPLC-UV: 237.6, 289.6 (t_R 15.65). ^{1}H- and ^{13}C-NMR: see [24]. GC/EI-MS: 428.9 (1), 355.1 (1), 334.2 (6, M^+), 302.3 (2), 281.1 (4), 266.9 (2), 253.0 (2), 216.1 (75, $[M - C_5H_8OS]^+$), 201.1 (30), 173.3 (14), 161.1 (100), 147.0 (15), 133.1 (17), 101.0 (29), 91.0 (17), 73.0 (16), 57.2 (18), 41.0 (35). HPLC-DAD/ESI-MS: 981.0 (1), 922.9 (1), 842.6 (1), 786.2 (1), 687.8 (1), 668.7 (3), 609.2 (1), 521.1 (1), 393.5 (1), 338.0 (2), 337.0 (6), 336.0 (20, $[M + 2\,H]^{2+}$), 335.0 (100, $[M + H]^+$), 265.4 (1), 218.4 (1), 217.4 (6), 189.5 (1), 147.2 (1), 87.3 (1).

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