Eremophilane Sesquiterpenoids from *Ligularia fischeri*

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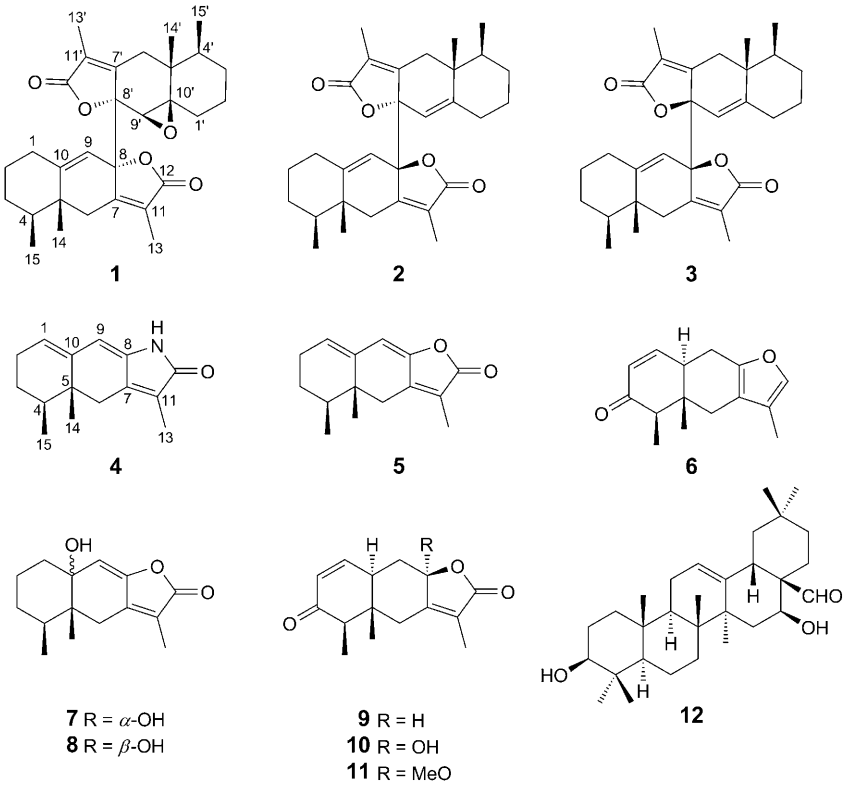
A novel eremophilane dimer, named as fischelactone, and a new sesquiterpene lactam, eremophila-1(10),7(11),8-triene-12,8-lactam, along with ten known compounds, were isolated from the roots of *Ligularia fischeri*. Their structures were established by means of spectroscopic analyses (EI-MS, HR-ESI-MS, IR, and 1D- and 2D-NMR data) and X-ray diffraction study.

Introduction. – The genus of *Ligularia* comprises *ca.* 150 species, most of which are distributed in China, and more than 27 species have long been used as traditional Chinese medicines [1]. As a rich source of eremophilane sesquiterpenoids responsible for the cytotoxicity of *Ligularia* plants, the secondary metabolites of this genus have been extensively investigated [2]. *Ligularia fischeri* (LEDEB.) TURCZ., a perennial plant, is distributed mainly in Northeast and Southwest China, Japan, Korea and in the far-east area of Russia. It is used as a folk medicine in China for the treatment of coughs, inflammations, jaundice, scarlet fever, rheumatoidal arthritis, and hepatic diseases [1]. Pharmacological research indicated that the extract of *L. fischeri* leaves is efficacious against collagen-induced arthritis in mice [3]. Furthermore, it was reported that furanoligularenone, a known eremophilane, would be responsible for the anti-inflammatory activities of this plant [4]. Previous phytochemical researches of this plant have led to the isolation of several eremophilane sesquiterpenoids [5–7]. In the course of searching for cytotoxic sesquiterpenoids from medicinal plants scattered in Northeast China, we reinvestigated the constituents of the roots of this plant, and obtained a novel eremophilane dimer, named as fischelactone (**1**)[1]), a new sesquiterpane lactam, eremophila-1(10),7(11),8-triene-12,8-lactam (**4**), along with nine known eremophilane sesquiterpenoids, **2**, **3** and **5**–**11**, and a triterpenoid **12**. Here, we describe the isolation and structure elucidation of these compounds.

Results and Discussion. – Compound **1** was obtained as colorless needles. The molecular formula $C_{30}H_{38}O_5$ was deduced by the *quasi*-molecular-ion peak at *m*/*z* 496.3061 ($[M+NH_4]^+$) in the HR-ESI-MS. The IR spectrum showed the absorption bands of C=C (1639 cm^{-1}) and α,β-unsaturated γ-lactone (1743 and 1616 cm^{-1}). Most signals in the ^1H- and ^{13}C-NMR (DEPT) spectra of **1** were displayed in pairs (*Table 1*), suggesting that **1** is a dimer of two sesquiterpene derivatives. Furthermore, the

[1]) Arbitrary numbering. For the systematic names, see *Exper. Part.*



significant ion fragments at *m/z* 247 ($[C_{15}H_{19}O_3]^+$), 230 ($[C_{15}H_{20}O_3 - H_2O]^+$), and 231 ($[C_{15}H_{19}O_2]^+$) in its EI-MS further confirmed the occurrence of two C_{15} units. The ^{1}H-NMR spectrum of **1** (*Table 1*) displayed signals of six Me groups at δ(H) 1.73 (*s*), 1.70 (*s*), 1.07 (*s*), 1.02 (*s*), 0.83 (*d*, $J = 6.5$), and 0.81 (*d*, $J = 6.5$), of an olefinic H-atom at δ(H) 5.60 (br. *s*, 1 H), and of an O-bearing CH group at δ(H) 3.20 (*s*, 1 H). The ^{13}C-NMR spectrum of **1** revealed resonances of 30 C-atoms, including the signals of two α,β-unsaturated γ-lactone moieties (δ(C) 158.7 (C(7)), 124.9 (C(11)), 172.4 (C(12)), 159.0 (C(7′)), 125.6 (C(11′)), 172.3 (C(12′))), of a trisubstituted C=C (δ(C) 115.3 (C(9)), 154.8 (C(10))), and of an epoxy group (δ(C) 63.6 (C(9′)), 66.1 (C(10′))). These data indicated that the structure of **1** is very similar to that of compound **2** [8], except for the presence of an epoxy group in **1** instead of a C=C bond in **2** (*Table 1*).

The constitution of **1** was established by its ^{1}H,^{1}H-COSY, gHMQC, and HMBC spectra. The ^{1}H,^{1}H-COSY spectrum showed a contiguous correlation of CH_2(1) to H−C(4), and of H−C(4) to Me(15). A long-range coupling between H−C(9) and CH_2(1) was also observed (*Fig. 1,a*). The HMBCs δ(H) 1.73 (Me(13))/δ(C) 158.7 (C(7)), 172.4 (C(12)), 124.9 (C(11)); δ(H) 1.07 (Me(14))/δ(C) 39.3 (C(4)), 45.4 (C(5)), 33.9 (C(6)), 154.8 (C(10)); δ(H) 0.83 (Me(15))/δ(C) 30.6 (C(3)), 39.3 (C(4)), 45.4 (C(5)), and the correlations δ(H) 5.60 (H−C(9))/δ(C) 32.6 (C(1)), 45.4 (C(5)), 158.7 (C(7)), 154.8 (C(10)) confirmed the presence of an eremophila-7(11),9-diene-

Table 1. *^{1}H- and ^{13}C-NMR* (DEPT) *Data of* **1** *in $CDCl_3$.* δ in ppm, J in Hz[a]).

	δ(H)	δ(C)		δ(H)	δ(C)
H_a–C(1)	2.19 (*ddd*, J = 13.0, 13.0, 4.0)	32.6 (*t*)	H_a–C(1′)	1.92 (*ddd*, J = 13.5, 13.0, 4.0)	30.4 (*t*)
H_b–C(1)	1.95 (br. *d*, J = 13.0)		H_b–C(1′)	0.96 (br. *d*, J = 13.5)	
H_a–C(2)	1.69–1.72 (*m*)	28.4 (*t*)	H_a–C(2′)	1.62–1.68 (*m*)	24.1 (*t*)
H_b–C(2)	1.07–1.12 (*m*)		H_b–C(2′)	1.14–1.18 (*m*)	
H_a–C(3)	1.28–1.34 (*m*)	30.6 (*t*)	H_a–C(3′)	1.22–1.28 (*m*)	29.9 (*t*)
H_b–C(3)	1.40–1.46 (*m*)		H_b–C(3′)	1.38–1.42 (*m*)	
H–C(4)	1.12–1.16 (*m*)	39.3 (*d*)	H–C(4′)	1.08–1.12 (*m*)	35.0 (*d*)
C(5)	–	45.4 (*s*)	C(5′)	–	43.5 (*s*)
H_a–C(6)	2.89 (*d*, J = 14.0)	33.9 (*t*)	H_a–C(6′)	2.44 (*d*, J = 14.0)	31.0 (*t*)
H_b–C(6)	2.29 (*d*, J = 14.0)		H_b–C(6′)	2.29 (*d*, J = 14.0)	
C(7)	–	158.7 (*s*)	C(7′)	–	159.0 (*s*)
C(8)	–	88.0 (*s*)	C(8′)	–	84.8 (*s*)
H–C(9)	5.60 (br. *s*)	153.1 (*d*)	H–C(9′)	3.20 (*s*)	63.6 (*d*)
C(10)	–	154.8 (*s*)	C(10′)	–	66.1 (*s*)
C(11)	–	124.9 (*s*)	C(11′)	–	125.6 (*s*)
C(12)	–	172.4 (*s*)	C(12′)	–	172.3 (*s*)
Me(13)	1.73 (*s*)	8.7 (*q*)	Me(13′)	1.70 (*s*)	9.0 (*q*)
Me(14)	1.07 (*s*)	20.5 (*q*)	Me(14′)	1.02 (*s*)	17.7 (*q*)
Me(15)	0.83 (*d*, J = 6.5)	16.3 (*q*)	Me(15′)	0.81 (*d*, J = 6.5)	15.9 (*q*)

[a]) Recorded at 500 MHz for ^{1}H-NMR and at 125 MHz for ^{13}C-NMR and DEPT.

12,8-lactone unit (*Fig. 1,a*). The other unit was analogously deduced from the ^{1}H,^{1}H-COSY and HMBC spectra (*Fig. 1,b*). The HMBCs δ(H) 1.70 (Me(13′))/δ(C) 159.0 (C(7′)), 172.3 (C(12′)), 125.6 (C(11′)); δ(H) 1.07 (Me(14′))/δ(C) 35.0 (C(4′)), 43.5 (C(5′)), 31.0 (C(6′)), 66.1 (C(10′)), and δ(H) 0.81 (Me(15′))/δ(C) 29.9 (C(3′)), 35.0 (C(4′)), 43.5 (C(5′)) also supported an eremophilanolactone skeleton. The^{1}H,^{1}H-COSY spectrum showed correlations of CH_2(1′) to H–C(4′), and of H–C(4′) to Me(15′) as well. The *singlet* at δ(H) 3.20 (H–C(9′)) in ^{1}H-NMR spectrum, together with the HMBCs δ(H) 3.20 (H–C(9′))/δ(C) 30.4 (C(1′)), 43.5 (C(5′)), 159.0 (C(7′)), 84.85 (C(8′)), 66.1 (C(10′)) allowed location of the epoxy group between C(9′) and C(10′). Thus, the unit B was deduced to be 9′,10′-epoxyeremophil-7′(11′)-ene-12′,8′-lactone (*Fig. 1*; unit B). By comparison with the ^{13}C-NMR data of reported eremophilane dimers [8][9], the connection of C(8)–C(8′) by a C–C bond could be deduced by the signals at δ(C) 88.0 and 84.8 ppm (both sp^3 quarternary C-atoms).

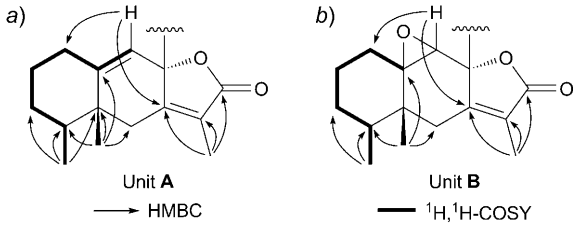


Fig. 1. *Key HMBCs and partial structures resolved by ^{1}H,^{1}H-COSY for* **1**

By biogenetic considerations of other eremophilane derivatives isolated from Compositae species, the relative orientation of Me(14) and Me(15) were both assigned to be β [10]. Hence, the Me(14), Me(15), Me(14′), and Me(15′) groups were all β-oriented. Fortunately, crystals of **1** were obtained by recrystallization from acetone and submitted to a single-crystal X-ray diffraction analysis. Due to the equivalent probability of the epoxy group being present in unit **A** or unit **B**, the X-ray structure of **1** (*Fig.* 2) showed two epoxy groups. In fact, there is only one epoxy group in compound **1**. More importantly, the X-ray structrue of **1** demonstrated the β-orientation of the epoxy group and the 8β/8β linkage of two units, and it also showed the β-orientation of Me(14), Me(15), Me(14′), and Me(15′) groups. Hence, the structure, including the relative configuration of **1**[1]), was unambiguously elucidated as shown in *Fig. 2*.

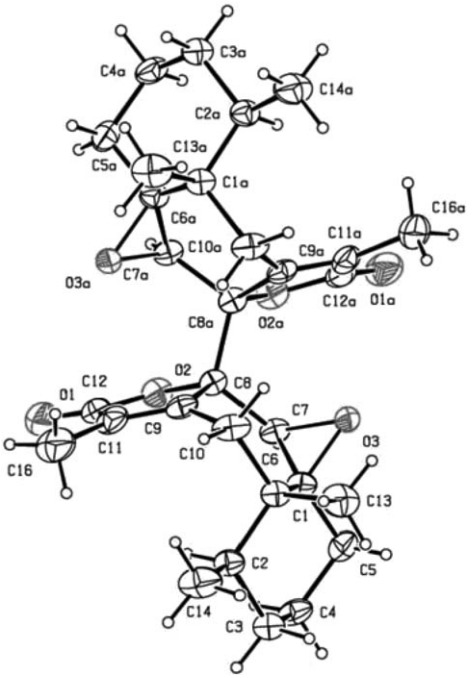


Fig. 2. *X-Ray single-crystal structure for* **1**

Compound **4** was obtained as colorless crystals. The HR-ESI-MS displayed the *quasi*-molecular-ion peak at *m*/*z* 230.1535 ($[M+H]^+$), providing the molecular formula $C_{15}H_{19}NO$. The IR spectrum showed the absorption bands of unsaturated C=O (1681 cm^{-1}), C=C (1638 cm^{-1}), and H−N (3176 cm^{-1}, sharp). The ^{1}H-NMR spectrum of **4** (*Table 2*) displayed the signals of three Me groups at δ(H) 1.81 (*d*, J = 1.5), 0.89 (*s*), and 0.92 (*d*, J = 7.0), which are characteristic of eremophilane derivatives isolated from *Ligularia* species [5][7]. In addition, there were signals of two olefinic H-atoms at δ(H) 5.64 (*dd*, J = 4.5, 4.0, H−C(1)) and 5.73 (br. *s*, H−C(9)), and a broad *singlet* at δ(H) 7.54 (br. *s*) attributed to the NH moiety. The ^{13}C-NMR (DEPT)

spectrum (*Table 2*) exhibited 15 C-atom signals, including those of an α,β-unsaturated C=O at δ(C) 173.1 (C(12)), and three C=C bonds at δ(C) 140.6 (C(7)), 125.0 (C(11)), 129.1 (C(1)), 134.6 (C(10)), 140.5 (C(8)), and 110.6 (C(9)). Except for the higher-field shifts of C(7) (from 147.3 to 140.6 ppm), C(8) (from 147.5 to 140.2 ppm), and C(10) (from 139.2 to 134.6 ppm; *Table 2*), the ^{13}C-NMR data of **4** are very similar to those of **5** (eremophila-1(10),7(11),8-triene-12,8-lactone; *Table 2*) [11]. The higher-field shifts were the results of replacement of the O-atom in **5** by the less electronegative N-atom in **4** [12]. The HR-ESI-MS spectrum confirmed the presence of a N-atom, and, consequently, compound **4** should have a lactam instead a lactone ring in **5**. Therefore, the structure of **4** is proposed to be eremophila-1(10),7(11),8-triene-12,8-lactam.

Table 2. *^{1}H- and ^{13}C-NMR* (DEPT) *Data of* **4** *and* **5** *in $CDCl_3$.* δ in ppm, *J* in Hz[a]).

	4		**5**	
	δ(H)	δ(C)	δ(H)	δ(C)
H–C(1)	5.64 (*dd*, *J* = 4.5, 4.0)	128.1 (*d*)	5.80 (*dd*, *J* = 4.0, 4.0)	131.2 (*d*)
CH_2(2)	2.13–2.18 (*m*)	25.1 (*t*)	2.21–2.26 (*m*)	26.1 (*t*)
CH_2(3)	1.46–1.51 (*m*)	25.6 (*t*)	1.54–1.59 (*m*)	26.5 (*t*)
H–C(4)	1.60–1.69 (*m*)	37.9 (*d*)	1.70–1.78 (*m*)	38.8 (*t*)
C(5)	–	36.8 (*s*)	–	37.7 (*s*)
H_a–C(6)	2.73 (*d*, *J* = 16.0)	33.6 (*t*)	2.82 (*d*, *J* = 16.0)	34.8 (*t*)
H_b–C(6)	2.10 (*d*, *J* = 16.0)		2.20–2.23 (*m*)	
C(7)	–	139.6 (*s*)	–	147.3 (*s*)
C(8)	–	139.5 (*s*)	–	147.5 (*s*)
H–C(9)	5.73 (br. *s*)	109.6 (*d*)	5.93 (br. *s*)	109.6 (*d*)
C(10)	–	133.6 (*s*)	–	139.2 (*s*)
C(11)	–	124.0 (*s*)	–	120.5 (*s*)
C(12)	–	172.1 (*s*)	–	171.6 (*s*)
Me(13)	1.81 (*d*, *J* = 1.5)	7.2 (*q*)	1.92 (*d*, *J* = 1.5)	8.5 (*q*)
Me(14)	0.89 (*s*)	14.6 (*q*)	0.97 (*s*)	15.7 (*q*)
Me(15)	0.92 (*d*, *J* = 7.0)	18.6 (*q*)	1.00 (*d*, *J* = 7.0)	19.6 (*q*)
NH	7.50–7.58 (br. *s*)	–	–	–

[a]) Recorded at 500 MHz for ^{1}H-NMR and at 125 MHz for ^{13}C-NMR and DEPT.

The coupling patterns of H–C(1) at δ(H) 5.64 (*dd*, *J* = 4.5, 4.0) and H–C(9) at δ(H) 5.73 (br. *s*), together with the HMBCs δ(H) 5.64 (H–C(1)/δ(C) 36.8 (C(5); δ(H) 5.73 (H–C(9)/δ(C) 139.6 (C(7)); and δ(H) 0.89 (Me(14)/δ(C) 133.6 (C(10) (*Fig. 3*), further confirmed the positions of two C=C bonds at C(1)(C(10)) and C(8). The NOESY correlations H_α–C(6)/H–C(4), H_β–C(6)/Me(13), H_β–C(6)/Me(14), and H_β–C(6)/Me(15), suggested the β-orientation of Me(14) and Me(15). Hence, the structure of **4** was established as eremophila-1(10),7(11),8-triene-12,8-lactam. To the best of our knowledge, this is the first eremophilane lactam isolated from *Ligularia* species, and it is the forth example of this type having been isolated from a natural source. The first three compounds were isolated from the rhizomes of *Petasites hybridus* [13], *Senecio flavus* [14], and *Senecio aegyptius* var. *discoideus* [12], respectively.

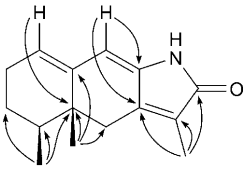


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Fig. 3. *Key HMBCs for* **4**

By comparing the spectral data with those reported in the literature, compounds **2**, **3**, and **5**–**12** were identified as 9β,9′α-bis-1,8-dihydroligularenolide [8], 9β,9′β-bis-1,8-dihydroligularenolide [8], eremophila-1(10),7(11),8-trien-12,8-olide [11], furanoligularenone [14], tsoongianolide A [8], tsoongianolide B [8], 3-oxoeremophila-1,7(11)-dien-12,8β-olide [14], 3-oxo-8α-hydroxy-10αH-eremophila-1,7(11)-dien-12,8β-olide [14], 3-oxo-8α-methoxy-10αH-eremophila-1,7(11)-dien-12,8β-olide [14], and gummosogenin [15].

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Experimental Part

General. TLC: silica gel GF_{254} (*Qingdao Marine Chemical Factory*, P. R. China). Column chromatography (CC): silica gel *G* (SiO_2; 200–300 and 300–400 mesh, *Qingdao Marine Chemical Factory*, P. R. China). M.p.: *Kofler* melting-point apparatus; uncorrected. Optical rotations: *Perkin-Elmer 341* polarimeter. IR Spectra: *Bruker Vertex 70* FT-IR spectrometer; in cm^{-1}. ^{1}H-, and ^{13}C-NMR (DEPT), and 2D-NMR spectra: *Bruker AVANCE 500* spectrometer; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI-MS: *HP-5988A GC/MS* instrument; in *m*/*z* (rel. %). HR-ESI-MS: *Bruker APEX- II* spectrometer.

Plant Material. The whole plants of *L. fischeri* were collected from Changbai Mountain, Tonghua, Jilin Province, P. R. China, in September 2008, and identified by Associate Prof. *Hong Zhao* (Marine College, Shandong University at Weihai). A voucher specimen (No. CB200809) was deposited with the Laboratory of Botany, Marine College, Shandong University at Weihai.

Extraction and Isolation. The powdered air-dried rhizomes of *L. fischeri* (8.2 kg) were extracted with petroleum ether (PE)/Et_2O/MeOH 1:1:1 three times (7 d each time) at r.t. The extract was concentrated to afford a residue (712 g), which was subjected to CC (SiO_2, 200–300 mesh, 2500 g; hexane/acetone 1:0, 20:1, 10:1, and 5:1): *Fractions A–D*. The main components of *Fr. A* and *Fr. B* (with hexane/acetone 1:0 and 20:1; 422 g) were an essential oil and colorless crystals. After filtration and recrystallization in acetone, **6** (126 g) was obtained from *Fr. A* and *Fr. B*. *Fr. C* (with hexane/acetone 10:1; 48 g) was subjected to CC (SiO_2, 800 g; hexane/acetone 20:1, 10:1, 5:1, and 3:1) to afford subfractions f_1–f_4. *Subfr.* f_1 (with hexane/acetone 20:1; 13 g) was subjected to CC (SiO_2; hexane/acetone 20:1 and 10:1) to obtained *Subfrs.* f_{1a} and f_{1b}. *Subfr.* f_{1a} (2.0 g) was purified by CC (SiO_2; hexane/AcOEt 50:1 and 30:1) to yield **2** (5 mg) and **3** (180 mg). *Subfr.* f_{1b} (1.5 g) was purified by CC (SiO_2; hexane/acetone 15:1) to afford **1** (26 mg). *Subfr.* f_2 (with hexane/acetone, 10:1; 17 g) was subjected to CC (SiO_2; hexane/acetone 20:1 to 3:1) to yield three subfractions: f_{2a}, f_{2b}, and f_{2c}. *Subfr.* f_{2a} (1.2 g) was purified by repeated CC (SiO_2; hexane/AcOEt 20:1) to give **7** (62 mg). Compound **8** (262 mg) was obtained from *Subfr.* f_{2c} (3.0 g) by recrystallization from acetone. *Subfr.* f_3 (with hexane/acetone, 5:1; 8.0 g) was subjected to CC (SiO_2; hexane/AcOEt 10:1, 5:1, and 3:1) to afford *subfrs.* f_{3a}, f_{3b}, and f_{3c}. *Subfr.* f_{3a} (1.0 g) was subjected to CC (SiO_2; hexane/AcOEt 10:1) to give a solid, and then purified by prep. TLC (hexane/Et_2O 5:1) to give **5** (R_f 0.38; 12 mg). Compound **11** (32 mg) was obtained from *Subfr.* f_{3b} (4 g) by CC (SiO_2; hexane/AcOEt 20:1). *Subfr.* f_{3c} (1.5 g) was purifed CC (SiO_2; hexane/AcOEt 30:1) to yield **12** (14 mg). *Subfr.* f_4 (with hexane/acetone, 3:1; 7.6 g) was subjected to CC (SiO_2; hexane/AcOEt 10:1, 5:1, and 3:1). After

repeated CC (SiO_2; hexane/AcOEt 10:1, 5:1, and 3:1), **4** (15 mg), **9** (27 mg), and **10** (18 mg) were obtained. There is no interesting compound in *Fr. D* (with hexane/acetone 5:1; 56 g).

Fischelactone (= rel-*(1a*R,*5*S,*5a*R,*9a*R,*9b*R*)-2,3,4,5,5a,6,9a,9b-Octahydro-5,5a,7-trimethyl-9a-[(4a*R,*5*S,*9a*S*)-4,4a,5,6,7,8-hexahydro-3,4a,5-trimethyl-2-oxonaphtho[2,3-*b*]furan-9a(2*H*)-yl]-8*H*-oxireno[1,8a]naphtho[2,3-*b*]furan-8-one*; **1**): Colorless crystals. M.p. 212–213°. $[\alpha]_D^{20} = +4$ ($c = 0.042$, $CHCl_3$). IR (KBr): 2918, 2847, 1743, 1639, 1616, 1446, 1150. ^{1}H- and ^{13}C-NMR: *Table 1*. EI-MS: 247 (8), 232 (22), 231 (95), 175 (10), 161 (14), 149 (12), 121 (10), 107 (11), 105 (16), 69 (44), 57 (53), 55 (72), 43(100), 41 (67). HR-ESI-MS: 496.3061 ($[M + NH_4]^+$, $C_{30}H_{42}NO_5^+$; calc. 496.3063).

X-Ray Crystal Data for **1**. See *Fig. 2*. $C_{30}H_{38}O_5$, M_r 478.60, 296 K, monoclinic, $P2_12_12_1$, $a =$ 17.5185(15) Å, $b = 6.9797(5)$ Å, $c = 12.8343(12)$ Å, $V = 1304.60(19)$ Å^3, $Z = 2$, $\mu(MoK_\alpha) = 0.086$ mm^{-1}, $\rho_{cal} = 1.249$ g cm^{-3}; crystal dimensions: $0.26 \times 0.32 \times 0.35$ mm; 11945 reflections measured ($\theta_{max} = 25.5$), 4035 were unique ($R_{int} = 0.023$), and of these 2974 had $I > 2\sigma(I)$ for which final $R1$, $wR2$ values were 0.0851 and 0.1437, resp., for 167 parameters. Data were collected using a *Bruker Smart Apex CCD* diffractometer using graphite-monochromated MoK_α radiation. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using *Bruker SHELXS-97*. The final R and R_w factors were 0.0529 and 0.1253, resp. CCDC-749697 contains the supplementary crystallographic data for **1**. The data can be obtained free of charge from *The Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

Eremophila-1(10),7(11),8-triene-12,8-lactam (= rel-*(4a*R,*5*S*)-1,4,4a,5,6,7-Hexahydro-3,4a,5-trimethyl-2*H*-benzo[f]indol-2-one*; **4**): Colorless crystal. M.p. 285–287°. $[\alpha]_D^{20} = -210$ ($c = 0.026$, acetone). IR (KBr): 3176 (N–H), 3012, 2954, 2929, 2891, 1681, 1638, 1613, 1447, 1380, 1339, 1249, 1147, 1065. ^{1}H- and ^{13}C-NMR: *Table 2*. HR-ESI-MS: 230.1535 ($[M + H]^+$, $C_{15}H_{20}NO^+$; calc. 230.1545).

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