Diversity of Sesquiterpenoids from *Carpesium cernuum*

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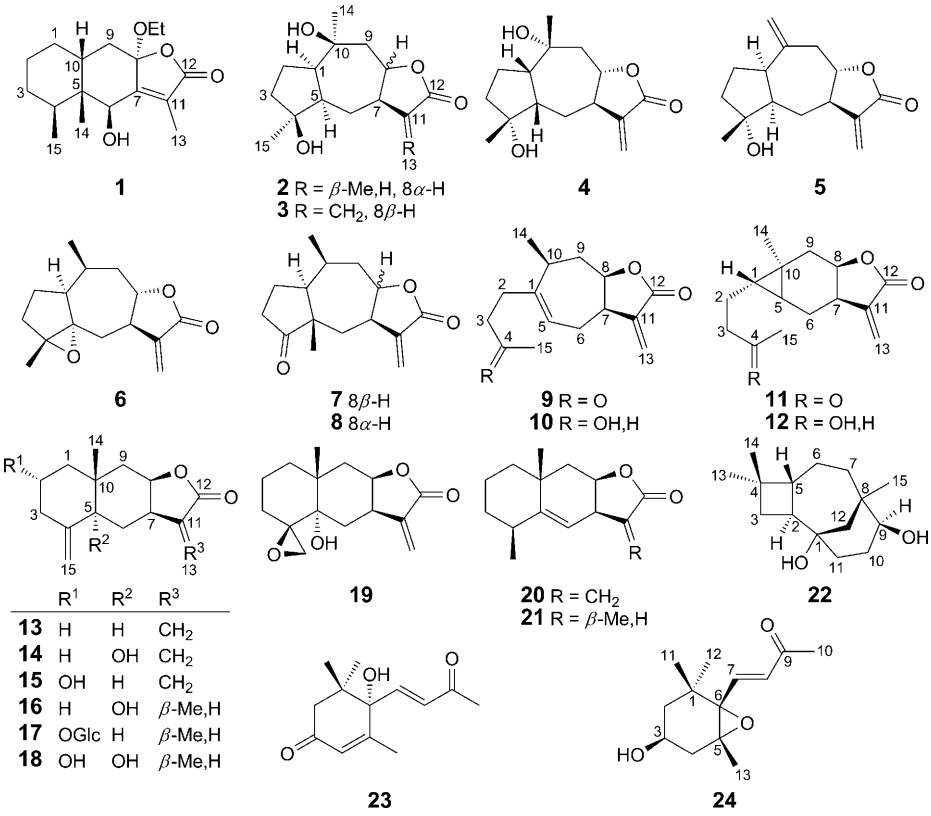
Two new sesquiterpene lactones, 6β-hydroxy-8α-ethoxyeremophil-7(11)-en-12,8β-olide (**1**) and 4β,10β-dihydroxy-1αH,5αH,11αH-guaian-12,8β-olide (**2**), together with 22 known sesquiterpenoids with various structural types, were isolated from *Carpesium cernuum* (Compositae). Their structures and configurations were elucidated by extensive 1D- and 2D-NMR spectroscopic analysis in combination with MS experiments, and comparison with literature data of related compounds.

Introduction. – Previous phytochemical studies indicate that sesquiterpene lactones are the most widespread secondary metabolites within the genus *Carpesium*. Different skeleton types of sesquiterpene lactones, such as eudesmanolides, guaianolides, xanthanolides, germacranolides, and carabranolides have already been isolated from the genus [1–6]. Noteworthy, some of them showed antifungal, antibacterial, and cytotoxic activities [7–10]. As a folk medicine with anti-inflammatory, pain-relief, and detoxification effects, *Carpesium cernuum* from other locations has been previously chemically investigated [11–14]. To study the influences that *C. cernuum* imposes on its environment concerning chemical aspects, as well as to search for further biologically active sesquiterpenoids from natural sources, we have reinvestigated the chemical constituents of *C. cernuum*. Interestingly, in our study, we have not detected germacrane sesquiterpenes, always found in the genus, which play a central role in the biosynthesis of guaiane- and eudesmane-type sesquiterpenes, but isolated a new eremophilenolide, 6β-hydroxy-8α-ethoxyeremophil-7(11)-en-12,8β-olide (**1**), and a new guaianolide, 4β,10β-dihydroxy-1αH,5αH,11αH-guaian-12,8β-olide (**2**), along with 22 known sesquiterpenoids, *i.e.*, 4β,10β-dihydroxy-1αH,5αH-guai-11(13)-en-12,8α-olide (**3**) [6], 4α,10α-dihydroxy-1βH,5βH-guai-11(13)-en-12,8α-olide (**4**) [6], 1-epi-inuviscolide (**5**) [15], 4α,5α-epoxy-10αH-1-epiinuviscolide (**6**) [9], 8-epiconfertin (**7**) [9], confertin (**8**) [15], 4*H*-xanthalongia (**9**) [16], xanthalongia (**10**) [16], carabone (**11**) [17], carabrol (**12**) [17], isoalantolactone (**13**) [11], telekin (**14**) [17], ivalin (**15**) [17], 11(13)-dihydrotelekin (**16**) [17], 2α-*O*-β-D-glucopyranosyleudesm-4(15)-en-12,8β-olide (**17**) [7], 2α,5α-dihydroxy-11αH-eudesm-4(15)-en-12,8β-olide (**18**) [7], 4(15)-β-epoxyisotelekin (**19**) [18], alantolactone (**20**) [11], 11(13)-dihydroalantolactone (**21**) [11], caryolane-1,9β-diol (**22**) [19], (+)-(*S*)-dehydrovomifoliol (**23**) [20], and (3*S*,5*R*,6*S*,7*E*)-5,6-epoxy-3-hydroxymegastigm-7-en-9-one (**24**) [20]. To the best of our knowledge, among these known sesquiterpenolides, compounds **3**–**10** and **19** have

been previously reported in some studies, but not for the species *C. cernuum*. In this article, we disclose the ^{13}C-NMR data of these compounds.

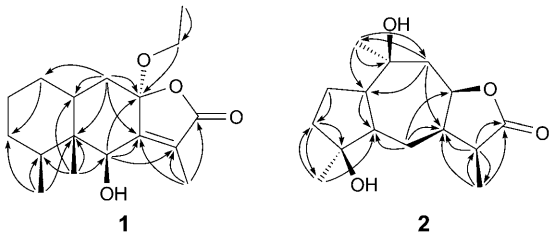


	R^1	R^2	R^3
13	H	H	CH_2
14	H	OH	CH_2
15	OH	H	CH_2
16	H	OH	β-Me,H
17	OGlc	H	β-Me,H
18	OH	OH	β-Me,H

Results and Discussion. – Compound **1** was isolated as a colorless gum. The molecular formula was determined to be $C_{17}H_{26}O_4$ by HR-ESI-MS (*m/z* 295.1906 ($[M + H]^+$)). The IR spectrum showed absorption bands for OH group (3456 cm^{-1}) and α,β-unsaturated-γ-lactone (1741 cm^{-1}). The ^{13}C-NMR and DEPT spectra of **1** exhibited 17 signals corresponding to four Me, five CH_2, three CH groups, and five quaternary C-atoms. Close inspection of the NMR data (*Table 1*) and comparing them with those of known eremophilanes indicated that compound **1** is an eremophilenolide [21]. In addition, the characteristic Me-group signals (δ(H) 2.06 (*d*, $J = 1.6$), 0.81 (*s*), 1.02 (*d*, $J = 7.2$), and δ(C) 8.89, 18.31, 15.59) for an eremophilene-type sesquiterpene lactone, further supported the above hypothesis. In the HMBC spectrum (*Fig. 1*), the correlations between Me(13) (δ(H) 2.06) and an ester CO group (C(12) (δ(C) 171.85)) and two olefinic C-atoms (C(7) (δ(C) 158.99) and C(11) (δ(C) 125.97) also showed that **1** was an eremophil-7(11)-en-12,8-olide, and an O-bearing H-atom (H–C(6) (δ(H) 5.02)) giving ^2J correlations to two quaternary C-atoms (C(5) (δ(C) 45.58) and C(7) (δ(C) 158.99)), and a ^3J correlation to C(11) (δ(C) 125.97) suggested that the OH group was at C(6). In addition, the Me group with the signal at δ(H) 1.18 exhibiting a ^3J

Table 1. *^{1}H- and ^{13}C-NMR Data of* **1** *and* **2**. At 400 and 100 MHz, respectively, in $CDCl_3$, δ in ppm, J in Hz. Assignments were confirmed by ^{1}H,^{1}H-COSY, HSQC, and HMBC experiments.

Position	**1**		**2**	
	δ(H)	δ(C) (DEPT)	δ(H)	δ(C) (DEPT)
1α	1.74–1.78 (*m*)	28.13 (*t*)	2.72 (*m*)	53.05 (*d*)
1β	1.31–1.35 (*m*)	–	–	–
2α	1.74–1.78 (*m*)	20.04 (*t*)	1.86 (*m*)	25.17 (*t*)
2β	1.20–1.22 (*m*)	–	1.47 (*m*)	–
3	1.39–1.42 (*m*)	28.62 (*t*)	1.70–1.75 (*m*)	37.41 (*t*)
4	1.31–1.35 (*m*)	31.75 (*d*)	–	82.75 (*s*)
5	–	45.58 (*s*)	1.82 (*m*)	53.48 (*d*)
6α	5.02 (*s*)	70.85 (*d*)	1.47 (*m*)	20.95 (*t*)
6β	–	–	1.00 (*ddd*, J = 13.6, 12.8, 12.4)	–
7	–	158.99 (*s*)	2.72 (*m*)	42.87 (*d*)
8	–	106.64 (*s*)	4.75 (*dt*, J = 10.0, 6.4)	79.14 (*d*)
9α	2.13 (*dd*, J = 14, 2.0)	37.74 (*t*)	2.22 (*ddd*, J = 14.4, 6.8, 1.2)	35.47 (*t*)
9β	1.83 (br. *d*, J = 14)	–	2.02 (br. *dd*, J = 14.4, 10.0)	–
10	1.31–1.34 (*m*)	36.05 (*d*)	–	73.18 (*s*)
11	–	125.97 (*s*)	2.89 (*dq*, J = 8.0, 7.6)	39.65 (*d*)
12	–	171.85 (*s*)	–	179.99 (*s*)
13	2.06 (*d*, J = 1.6)	8.90 (*q*)	1.16 (*d*, J = 7.2)	10.14 (*q*)
14	0.81 (*s*)	18.32 (*q*)	1.27 (*s*)	33.11 (*q*)
15	1.02 (*d*, J = 7.2)	15.60 (*q*)	1.34 (*s*)	25.45 (*q*)
1′	3.47 (*q*, J = 7.2), 3.38 (*q*, J = 7.2)	58.5 (*t*)	–	–
2′	1.18 (*t*, J = 7.2)	15.3 (*q*)	–	–



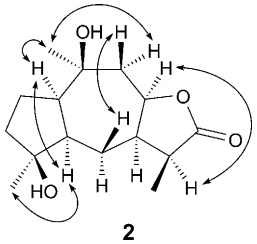
1 **2**

Fig. 1. *Key gHMBCs* (H → C) *of* **1** *and* **2**

correlation to C(8) (δ(C) 106.64) showed that an EtO group could be at C(8). The relative configuration was determined by NOE experiments and empirical rules. In a number of 8α-methoxyeremophilenolide derivatives bearing the *cis*-fused carbocyclic ring system, the chemical shifts due to the angular Me(14) groups which appeared at δ(H) 0.80, are downfield from those due to Me(15), whereas this relationship is reversed in the 8β-derivatives [21][22]. Thus, **1** should be a 8α-derivative with a *cis*-fused carbocyclic ring system, since Me(14) and Me(15) resonated at δ(H) 0.81 and 1.02, respectively. This can be confirmed by the negative optical rotation, $[\alpha]_D^{20} = -29$ (c = 0.20, $CHCl_3$), for **1** having a non-steroidal conformation [22]. The Me(14) and Me(15) groups are β-oriented as expected for biogenetic reasons [23]. This was

confirmed by the enhanced signals of Me(14) and H–C(10) on irradiation of Me(15) in the nuclear *Overhauser* enhanced differential (NOED) spectrum. And HO–C(6) was also β-oriented as suggested by the presence of a homoallylic spin coupling (1.6 Hz) between H_α–C(6) and Me(13) [21]. The NMR data of **1** are in agreement with the empirical rules reported by *Sugama et al.* [21] and *Naya et al.* [22]. Thus, compound **1** is determined as 6β-hydroxy-8α-ethoxyeremophil-7(11)-en-12,8β-olide, which must be an artifact from the extraction procedure with EtOH. However, the underlying lactol was shown indirectly to be present in the genus *Carpesium* for the first time.

Compound **2** was isolated as a colorless oil, and the molecular formula of $C_{15}H_{24}O_4$ was determined by HR-ESI-MS (*m*/*z* 291.1560 ($[M + Na]^+$)). The IR spectrum indicated absorptions for OH (3411 cm^{-1}) and a γ-lactone C=O (1757 cm^{-1}). The ^{13}C-NMR spectrum displayed signals of 15 C-atoms, including a C=O group, two O-bearing quaternary C-atoms, one O-bearing CH group, and three Me and four CH_2 groups, assigned by HSQC, HMBC, and DEPT-135 experiments. The ^{1}H- and ^{13}C-NMR signals (*Table 1*) provided evidence to suggest that compound **2** is a guaianolide, due to the similarity of the spectral data, when compared with those of compound **3** [6], except for the absence of a C=C bond between C(11) and C(13). Thus, compound **2** was deduced to possess an 11(13)-dihydroguaianolide skeleton. The ^{1}H-NMR spectrum (*Table 1*) showed the *H*–C–OH signal at δ(H) 4.75 (*dt*) and two *singlet* Me signals at δ(H) 1.27 (*s*) and 1.34 (*s*), suggesting that two OH groups were at C(4) (δ(C) 82.75) and C(10) (δ(C) 73.18). In the HMBC spectrum of **2** (*Fig. 1*), the correlations between δ(H) 1.27 (Me(14)) and δ(C) 53.05 (C(1)), 35.47 (C(9)), and 73.18 (C(10)), together with the correlations between δ(H) 1.34 (Me(15)) and δ(C) 37.41(C(3)) and 53.48 (C(5)), and between δ(H) 1.16 (Me(13)) and δ(C) 42.87 (C(7)), 39.65 (C(11)), and 179.99 (C(12)) further confirmed the above deduction. The relative configuration of **2** was established by ^{1}H-NMR and NOESY experiments. In the ^{1}H-NMR spectrum (*Table 1*), the coupling constant between H–C(8) (δ(H) 4.75) and H–C(7), J(8,7) = 6.4 Hz, helped us to determine the relative *cis*-configuration of the lactone ring, and the J value for H–C(9) (δ(H) 2.22) (J(9,8) = 6.8 Hz) placed the H-atom in an α-orientation. In the NOESY experiment (*Fig. 2*), cross-peaks between H_α–C(8) and H–C(11), along with NOE correlations between H_α–C(9) (δ(H) 2.22) and Me(14), established them to be on the same side (α), whereas H_β–C(9) (δ(H) 2.02) and H–C(6) (δ(H) 1.00) are on the β-face. The large coupling constant for H_β–C(6) (δ(H) 1.00)/H–C(5), J(6,5) = 12.4 Hz, indicated an α-orientation of H–C(5). An NOE between H_α–C(5) and Me(15) implied a β-orientation for OH–C(4). As the chemical shifts of H–C(1) and H–C(7) were overlapping, it is



2

Fig. 2. *Key NOESY correlations* (H ↔ H) *of* **2**

difficult to measure the coupling constants of H–C(7) and H–C(1). However, the Me(14) gave a strong cross-peak to H–C(1) or H–C(7), and a molecular model of this molecule showed that H–C(7) was far from the Me(14), indicating α-orientation for H–C(1). This was further confirmed by a correlation between H–C(1) and H–C(5). From these data, the chemical structure of **2** was determined as 4β,10β-dihydroxy-1αH,5αH,11αH-guaian-12,8β-olide.

Table 2. *^{13}C-NMR Data of* **3**–**10** *and* **19**. In $CDCl_3$ or (D_6)acetone, δ in ppm.

	3[a])[b])	**4**[a])	**5**[a])	**6**[c])	**7**[c])	**8**[a])	**9**[c])	**10**[c])	**19**[a])
1	52.78	52.14	56.52	47.64	46.85	45.84	145.44	144.19	34.42
2	25.21	23.60	24.38	28.83	24.12	21.22	26.43	26.33	19.35
3	38.97	41.12	39.55	32.64	34.80	36.48	37.81	37.77	29.02
4	80.75	80.49	80.11	69.91	221.05	219.19	67.67	208.07	61.27
5	50.73	50.06	50.86	69.70	50.78	50.53	119.45	119.89	74.09
6	29.00	29.23	29.94	30.48	34.90	35.81	32.79	30.20	29.11
7	43.53	50.80	42.15	44.31	45.08	38.98	41.97	41.88	37.30
8	83.40	79.19	81.25	82.49	80.80	79.36	79.36	79.28	76.68
9	44.89	48.64	40.19	40.32	41.46	37.93	36.49	36.44	34.42
10	72.95	73.32	177.71	34.51	32.32	30.57	34.93	35.20	36.79
11	142.30	140.16	139.86	138.99	139.95	139.29	138.89	138.78	141.68
12	170.78	170.22	169.91	169.9	169.87	123.29	170.28	170.07	170.55
13	118.80	118.84	122.76	119.77	120.26	169.40	121.96	121.93	120.61
14	31.35	25.50	111.90	14.54	16.95	17.26	20.78	20.76	21.66
15	24.38	23.05	24.55	15.44	23.34	20.03	23.11	29.76	54.41

[a]) Recorded at 100 MHz. [b]) Recorded in (D_6)acetone. [c]) Recorded at 75 MHz.

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Experimental Part

General. Column chromatography (CC): silica gel (SiO_2; 200–300 mesh) from *Qingdao Marine Chemical Factory*, Qingdao, P. R. China. TLC: Silica gel GF_{254} (10–40 μm) from *Qingdao Marine Chemical Factory*; detection at 254 nm, and by heating after spraying with 5% H_2SO_4 in EtOH (*v*/*v*). Optical rotations: *Perkin-Elmer 341* polarimeter; in $CHCl_3$ at 20°. UV Spectra: *NewCentury Pgeneral T6* spectrophotometer; λ_{max} in nm. IR Spectra: *Nicolet-NEXUS-670* FT-IR spectrometer; with KBr pellets; in cm^{-1}. NMR Spectra: *Bruker AVANCE III-400* NMR and *Varian-Mercury-300BB* instruments; δ in ppm rel. to Me_4Si, *J* in Hz. EI-MS: *HP 5988A* GC/MS instrument; in *m*/*z* (rel. %). HR-ESI-MS: *Bruker APEX-II* instrument; in *m*/*z* (rel. %).

Plant Material. The whole plant of *Carpesium cernuum* was collected from Tulugou, Gansu Province of China, in August 2006, and was identified by Adjunct Prof. *Huan-Yang Qi*, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences. A voucher specimen for this material (No. 2006C02) has been deposited with the Key Laboratory for Natural Medicine of Gansu Province, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences.

Extraction and Isolation. The air-dried whole plant (3.9 kg) was pulverized and extracted with 95% EtOH (4 × 20 l) at r.t. for 5 d each time. The combined extracts were evaporated to dryness under

reduced pressure. The resulting residue (321 g) was suspended in H_2O (1.5 l), and extracted with petroleum ether (PE; 60–90°, 3 × 1.5 l), AcOEt (3 × 1.5 l), and BuOH (3 × 1.5 l), resp. The PE extract (54.7 g) was subjected to CC on SiO_2 (600 g) with a gradient of PE/acetone (40:1 → 1:2 (*v*/*v*)) to afford eight fractions, F_1–F_8, after TLC analysis. F_2 (365 mg) and F_3 (562 mg) were rechromatographed on SiO_2 (11 and 17 g, resp.) with PE/AcOEt 20:1 to give two ($F_{2\text{-}1}$ and $F_{2\text{-}2}$) and three fractions ($F_{3\text{-}1}$–$F_{3\text{-}3}$), resp. $F_{2\text{-}2}$ (26 mg) was further separated by CC on SiO_2 (1 g) eluting with PE/acetone 10:1 to yield **1** (5.5 mg); $F_{3\text{-}1}$ (1.2 g) was rechromatographed on SiO_2 (30 g) with PE/$CHCl_3$ 4:1 to give two subfractions, $F_{3\text{-}1\text{-}1}$ and $F_{3\text{-}1\text{-}2}$. Then, $F_{3\text{-}1\text{-}1}$ was separated by CC on SiO_2 (450 mg) with PE/acetone 15:1 to provide **14** (20 mg); and $F_{3\text{-}1\text{-}2}$ (66 mg) was crystallized in acetone to yield **11** (30 mg). Part of $F_{3\text{-}2}$ was further purified by prep. TLC (PE/acetone 6:1) to give **16** (10 mg). $F_{3\text{-}3}$ (360 mg) was rechromatographed on SiO_2 (24 g) with PE/acetone 15:1 to yield $F_{3\text{-}3\text{-}1}$ and $F_{3\text{-}3\text{-}2}$; then, $F_{3\text{-}3\text{-}1}$ (45 mg) was further separated by CC on SiO_2 (1.8 g) with PE/AcOEt 10:1 to give a mixture of **8** and **10**; and $F_{3\text{-}3\text{-}2}$ was processed by prep. TLC ($CHCl_3$/AcOEt 7:1.5) to yield a mixture of **7** and **11**. F_4 (1.6 g) was separated by CC on SiO_2 (30 g) eluting with PE/acetone 12:1 to yield three fractions, $F_{4\text{-}1}$–$F_{4\text{-}3}$. $F_{4\text{-}1}$ (230 mg) was purified by repeated CC on SiO_2 with PE/acetone 12:1 to provide **12** (15 mg) and **15** (20 mg); and $F_{4\text{-}2}$ yielded **24** (4.2 mg) after prep. TLC (PE/$CHCl_3$ 5:2). The AcOEt extract (53.5 g) was chromatographed on SiO_2 (600 g) eluting with PE/acetone (30:1 → 1:1 (*v*/*v*)) to give seven fractions, M_1–M_7. In the fraction M_1, compounds **13** (10 mg), **20** (12 mg), and **21** (10 mg) were processed by prep. TLC ($CHCl_3$/PE 1:3), resp. M_2 (1.1 g) was further separated by CC on SiO_2 (20 g) with PE/AcOEt 12:1 to give two subfractions, $M_{2\text{-}1}$ and $M_{2\text{-}2}$; then, $M_{2\text{-}2}$ (125 mg) was subjected to SiO_2 (4 g) eluting with PE/acetone 15:1 to yield impure compounds **6** and **19**, which were purified by repeated CC on SiO_2 with $CHCl_3$/AcOEt 25:1 to give **6** (10 mg) and **19** (8.9 mg). *Fr.* M_3 (2.4 g) was subjected to CC on SiO_2 (60 g) with PE/acetone 8:1 to afford three subfractions, $M_{3\text{-}1}$, $M_{3\text{-}2}$, and $M_{3\text{-}3}$. $M_{3\text{-}1}$ (189 mg) yielded **5** (13.2 mg) and **8** (11.3 mg) after CC on SiO_2 (15 g) with $CHCl_3$/AcOEt 18:1, and compound **9** was obtained as part of a mixture of **12** from this fraction after prep. TLC ($CHCl_3$/acetone 6:1). $M_{3\text{-}2}$ (87 mg) isolated over a SiO_2 column (2.5 g) with PE/acetone 3:1 afforded **22** (8.4 mg) and **23** (6.3 mg), which were purified by CC on SiO_2 with $CHCl_3$/acetone 8:1. M_4 (4.2 g) was chromatographed on a SiO_2 column (60 mg) using $CHCl_3$/AcOEt 1:1 to give four subfractions, $M_{4\text{-}1}$–$M_{4\text{-}4}$. $M_{4\text{-}1}$ (1.2 g) was rechromatographed on SiO_2 (30 g) eluting with $CHCl_3$/acetone 8:1 to yield **3** (13.4 mg) and **4** (21.3 mg), which were purified by CC on SiO_2 with $CHCl_3$/AcOEt 1:1. $M_{4\text{-}2}$ (236 mg) yielded **18** (13.2 mg) after CC on SiO_2 (6 g) with PE/acetone 4:1 and prep. TLC (PE/acetone 2:1). $M_{4\text{-}3}$ (150 mg) was rechromatographed on SiO_2 (3.5 g) with PE/acetone 2:1 to afford **2** (18.3 mg), which was purified by CC on SiO_2 with $CHCl_3$/AcOEt 1:1. The BuOH extract (54.1 g) was chromatographed on SiO_2 (600 g), eluting with $CHCl_3$/MeOH, gradually increasing volumes of MeOH to obtain six fractions: D_1 (30:1; 3000 ml), D_2 (15:1; 3000 ml), D_3 (10:1; 3000 ml), D_4 (7:1; 3000 ml), D_5 (5:1; 3000 ml), and D_6 (1:1; 3000 ml). *Fr.* D_2 (2.1 g) was further fractionated on a SiO_2 column (28 g) with $CHCl_3$/MeOH (15:1; 1000 ml) to give two subfractions, $D_{2\text{-}1}$ and $D_{2\text{-}2}$. $D_{2\text{-}2}$ (812 mg) was further purified by repeated CC on SiO_2 with $CHCl_3$/MeOH 15:1 to afford **17** (33 mg).

6β-Hydroxy-8α-ethoxyeremophil-7(11)-en-12,8β-olide (=*(4*R*,4a*S*,5*R*,8a*S*,9a*S*)-9a-Ethoxy-4a,5,6,7,8,8a,9,9a-octahydro-4-hydroxy-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one*; **1**). Colorless gum. UV (MeOH): 230. $[\alpha]_D^{20} = -29$ ($c = 0.20$, $CHCl_3$). IR (KBr): 3456, 2923, 2855, 1741, 1462, 1380, 1306, 1177, 1146, 988, 935. ^{1}H- and ^{13}C-NMR: *Table 1*. EI-MS: 294 (0.8, M^+), 276 (1.0), 248 (4.8), 230 (2.1), 221 (3.5), 170 (23.3), 142 (30.6), 109 (54.2), 95 (35.6), 81 (23.7), 67 (48.1), 55 (49.3), 43 (100). HR-ESI-MS: 295.1906 ($[M + H]^+$, $C_{17}H_{27}O_4^+$; calc. 295.1909).

*4β,10β-Dihydroxy-1α*H*,5α*H*,11α*H*-guaian-12,8β-olide* (=*(3*R*,3a*S*,4a*S*,5*R*,7a*S*,8*R*,9a*S*)-Deca-hydro-5,8-dihydroxy-3,5,8-trimethylazuleno[6,5-*b*]furan-2(3*H*)-one*; **2**). Colorless oil. UV (MeOH): 226. $[\alpha]_D^{20} = +44$ ($c = 0.15$, $CHCl_3$). IR (KBr): 3411, 2964, 2929, 2858, 2252, 1757, 1461, 1376, 1202, 1170, 909, 734, 649. ^{1}H- and ^{13}C-NMR: *Table 1*. EI-MS: 250 (1.0, $[M - H_2O]^+$), 235 (0.3), 217 (0.2), 207 (0.5), 193 (1.5), 95 (17.0) 84 (21.3), 71 (28.8), 57 (35.4), 43 (100). HR-ESI-MS: 291.1560 ($[M + Na]^+$, $C_{15}H_{24}NaO_4^+$; calc. 291.1572).

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