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Four New Guaianolides and Acetylenic Alcohol from *Saussurea katochaete* Collected in China

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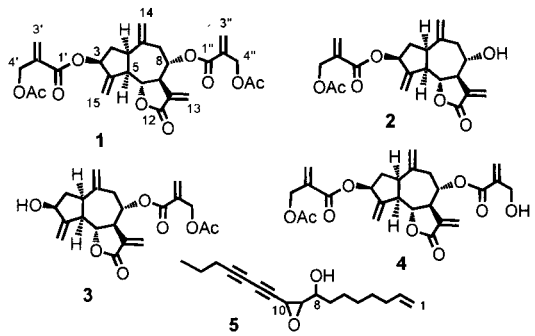
Four new guaianolides and an acetylenic alcohol were isolated from *Saussurea katochaete* (Asteraceae) collected in China. The structures were determined based on the spectroscopic data including the absolute configuration by application of advanced Mosher's method.

Keywords: *Saussurea katochaete*, Asteraceae, Guaianolides, Acetylenic alcohol, Sesquiterpenes.

The area of Hengduan Mountains in China is very interesting from the view point of plant diversity. The intra-specific diversity of some *Ligularia* species collected in this area have been found and we have published some results [1-8]. The *Saussurea* species are known to produce many kinds of sesquiterpenoids and show interesting biological activities, icluding inhibition of TNF-α [9-11]. In connection with the studies on chemical substances of the Asteraceae family, we had a chance to collect *Saussurea katochaete* in 2009 in China [12,13]. Four new guaianolides, **1**, **2**, **3**, and **4**, from the leaves, and new enediynol **5** from the root were isolated, along with known compounds **6-14**. Now we report our results of this study in detail.



Compound **1** showed a quasi molecular ion peak at *m/z* 515 and its molecular formula was determined to be $C_{27}H_{30}O_{10}$ by HRCIMS. The IR spectrum indicated the presence of carbonyl groups (1769, 1745, and 1726 cm^{-1}), the number of which was five, being supported by the ^{13}C NMR data (δ 164.2, 165.0, 168.1, 169.5, and 169.6). The ^{1}H NMR spectrum showed the presence of five exomethylene groups (δ_H 4.65, 4.72; 5.34, 5.53; 5.33, 6.13; 5.51, 6.34; 5.50, 6.24), two acetyl groups (δ 1.64, 1.67), three oxymethine protons, and two oxymethylene groups (Table 1). The ^{13}C NMR and HSQC spectra suggested the presence of two methyl, nine methylene, six methine, and ten quaternary carbon signals (Table 2). Considering the existence of above mentioned ten double bonds and thirteen degrees of unsaturation, this molecule should be tricyclic. The HMBC spectrum indicated correlations between H-1 and C-5, C-6 and C-9, between H-14 and C-1, between H-13 and C-7, C-11, and C-12, and between H-15 and C-5. From these observations along with COSY correlations, a guaiane-type skeleton was established for this compound (Figure 1). Both esters were determined as acetoxymethacrylates by further correlations shown in Figure 1. The position of substitution was determined by the HMBC correlation between H-3 and C-1'. However, the correlation between H-8 and C-1" was not observed. Therefore it is not clear if this is 12,6-olide or 12,8-olide. The chemical shifts for C-8 and C-6 are δ 74.5 and 77.1, respectively, and this can not give a definite difference, either. However, the position of the ester was assigned at C-8 and the lactone was 12,6-olide, because the NOE between H-13E and H-8 was observed (Figure 1). If this is the other way, this NOE should not be observed. The stereochemistry was determined by the NOESY spectrum as shown in Figure 1. Because the NOE between H-1 and H-5 was observed, rings A and B should be *cis* fused. The NOE correlations between H-5 and H-7, between H-6 and H-2β, H-8β, and H-9β, and between H-1 and H-3 were observed and the configuration was established as depicted in the formula.

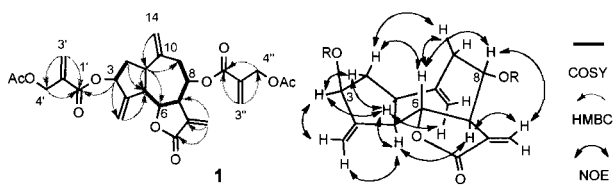


Figure 1: Selected COSY, HMBC, and NOE correlations for compound **1**.

Compound **2** showed a quasi molecular ion peak at *m/z* 389 and the molecular formula was determined to be $C_{21}H_{24}O_7$ by HRCIMS. The ^{1}H and ^{13}C NMR spectra indicated that this compound has only one acetyl group as well as two other carbonyl groups (Tables 1 and 2). The absorption at 3502 cm^{-1} (OH) along with 1765, 1745, and 1726 cm^{-1} (three carbonyl groups) was observed in its IR spectrum. The guaiane skeleton was indicated by the COSY and HMBC correlations (Figure 2). The positions of the hydroxy group and the ester moiety were determined at C-8 and C-3, respectively, judging from the COSY correlation between H-8 and OH signals as well as the chemical shifts for H-8, H-3, C-8, and C-3 (Tables 1

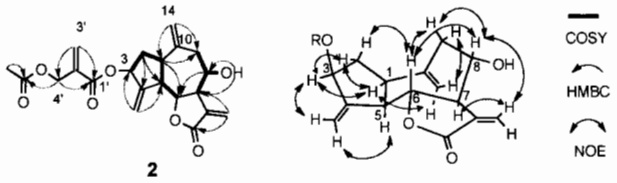


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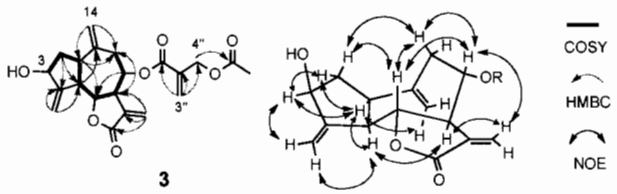
Figure 2: Selected COSY, HMBC, and NOE correlations for compound **2**.



3

Figure 3: Selected COSY, HMBC, and NOE correlations for compound **3**.

Table 1. ^{1}H NMR data for compounds **1-4** (500 MHz, in C_6D_6) (mult, *J* in Hz)

Position	1	2	3	4
1	2.21 (dt, 11.2, 7.8)	2.23 (ddd, 10.4, 8.8, 7.6)	2.25 (ddd, 11.2, 8.6, 7.4)	2.21 (ddd, 11.2, 8.2, 7.5)
2	1.95 (dt, 13.4, 7.8)	1.99 (dt, 13.3, 7.6)	1.72 (dt, 13.0, 7.4)	1.95 (dt, 13.5, 7.5)
	1.46 (ddd, 13.4, 11.2, 7.8)	1.53 (ddd, 13.3, 10.4, 7.6)	1.34 (ddd, 13.0, 11.2, 7.4)	1.46 (ddd, 13.5, 11.2, 7.5)
3	5.55 (tt, 7.8, 2.0)	5.57 (tt, 7.6, 2.0)	4.11 (br t, 7.4)	5.56 (tt, 7.5, 1.8)
5	2.07-2.12 (m)	2.12 (dd, 10.3, 8.8)	2.15 (dd, 10.5, 8.6)	2.10 (dd, 10.4, 8.2)
6	3.41 (dd, 10.4, 9.2)	3.47 (dd, 10.3, 9.1)	3.45 (dd, 10.5, 9.2)	3.42 (dd, 10.4, 9.3)
7	2.50 (tt, 9.2, 3.3)	2.15 (tt, 9.1, 3.3)	2.54 (tt, 9.2, 3.2)	2.50 (tt, 9.3, 3.2)
8	4.76-4.80 (m)	3.19 (ddt, 9.1, 7.0, 4.8)	4.76 (ddd, 9.2, 5.2, 3.8)	4.77 (ddd, 9.3, 5.0, 4.2)
9	2.10 (dd, 14.7, 5.0)	1.96 (dd, 13.7, 4.8)	2.16 (dd, 14.6, 5.2)	2.11 (dd, 14.7, 5.0)
	1.98 (dd, 14.7, 4.1)	1.63 (dd, 13.7, 4.8)	2.02 (dd, 14.6, 3.8)	1.98 (dd, 14.7, 4.2)
13	6.13 (d, 3.3)	6.29 (dd, 3.3, 1.3)	6.14 (d, 3.2)	6.14 (d, 3.2)
	5.33 (d, 3.3)	5.92 (dd, 3.3, 1.3)	5.33 (d, 3.2)	5.34 (d, 3.2)
14	4.72 (s)	4.71 (d, 1.6)	4.77 (s)	4.71 (s)
	4.65 (s)	4.61 (d, 1.6)	4.65 (s)	4.65 (s)
15	5.53 (d, 2.0)	5.55 (dd, 2.0, 1.7)	5.48 (s)	5.53 (d, 1.8)
	5.34 (d, 2.0)	5.34 (dd, 2.0, 1.7)	5.22 (s)	5.34 (d, 1.8)
3'	6.34 (s)	6.33 (s)	-	6.34 (s)
	5.51 (s)	5.49 (s)	-	5.50 (s)
4'	4.89 (d, 13.4)	4.87 (d, 13.4)	-	4.89 (d, 13.3)
	4.81 (d, 13.4)	4.79 (d, 13.4)	-	4.81 (d, 13.3)
3"	6.24 (s)	-	6.24 (s)	6.14 (s)
	5.50 (s)	-	5.49 (s)	5.58 (s)
4"	4.78 (s)	-	4.78 (s)	4.13 (d, 5.9)
4'-Ac	1.67 (3H, s)	1.66 (3H, s)	-	1.67 (s)
4"-Ac	1.64 (3H, s)	-	1.64 (s)	-
OH	-	0.97 (d, 7.0)	1.28-1.37 (br s)	1.36 (d, 5.9)

and 2). The NOE correlations indicated that configurations were the same as those of compound **1**.

Compound **3** had the same molecular formula as that of **2**. The COSY and HMBC spectra revealed that C-3 is substituted with a hydroxy group, and C-8 is with acetoxymethacrylate as shown in Figure 3. The stereochemistry was also the same as those of compounds **1** and **2**.

Jang et al reported that they isolated a compound with the same skeleton, but has a lactone fused at C-7 and C-8 with an ester at C-6 without any evidence [14-16]. Because we have observed an NOE between H-13E and H-8 for compounds **1-3**, we have enough reason to conclude these structures.

The molecular formula of compound **4** was $C_{25}H_{28}O_9$ (by HRCIMS). The presence of a hydroxy group (3470 cm^{-1}) as well as carbonyl groups (1765 and 1728 cm^{-1}) was shown by the IR spectrum. The ^{1}H and ^{13}C NMR spectra are very similar to those of

Table 2. ^{13}C NMR data for compounds **1-4** (125 MHz, in C_6D_6)

Carbon	1	2	3	4
1	45.2	45.2	45.2	45.2
2	36.3	36.5	39.3	36.3
3	75.3	75.5	73.6	75.3
4	147.5	147.8	152.8	147.5
5	51.0	51.1	51.0	51.0
6	77.1	77.6	77.7	77.1
7	47.2	50.7	47.3	47.3
8	74.5	71.9	74.6	74.2
9	36.9	41.7	36.9	37.0
10	141.7	142.7	142.4	141.8
11	138.4	139.2	138.6	138.3
12	168.1	168.8	168.2	168.1
13	121.2	121.9	121.0	121.3
14	117.7	116.5	117.3	117.7
15	115.7	115.3	112.8	115.6
1'	165.0	164.9	-	165.0
2'	136.3	136.3	-	136.3
3'	128.0	128.1	-	128.0
4'	62.5	62.5	-	62.5
1"	164.2	-	164.2	165.0
2"	136.1	-	136.1	140.3
3"	128.5	-	128.4	125.3
4"	62.3	-	62.3	61.9
4'-Ac	169.6	169.6	-	169.6
4'-Ac	20.3	20.3	-	20.3
4"-Ac	169.5	-	169.5	-
4"-Ac	20.3	-	20.3	-

compound **1**, except that this compound has one acetyl group and one hydroxy group, instead. The COSY and HMBC correlations indicated that this compound has the same skeleton and it has two different ester groups at C-3 and C-8 positions. Therefore, these data suggested that one acetoxy group of either ester in compound **1** was replaced by OH. Unfortunately, no correlation between H-3 or H-8 and the corresponding ester carbonyl group was observed in the HMBC spectrum. However, it is possible to assign which ester is attached at C-3 or C-8 by comparing the chemical shifts for the ester part with those of compounds **2** and **3**. In the case of compound **2** (C-3 ester), the oxymethylene signals (H-4') are at δ 4.87 and 4.79, while they are at δ 4.78 (2H, H-4") for compound **3** (C-8 ester). In compound **1**, they are almost the same chemical shifts and this assumption received support (Table 1). In the case of compound **4**, those at δ 4.89 and 4.81 should be for the C-3 ester (with Ac) and those at δ 4.13 (2H) should be for the hydroxymethylacrylate at C-8 (Table 1). The stereochemistry was established by the NOESY spectrum as depicted in the Figure 4.

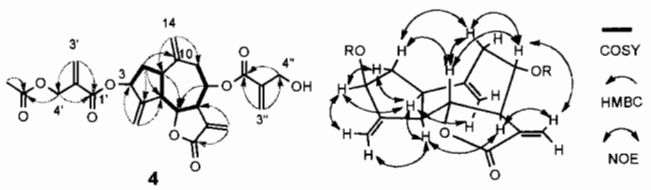


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Figure 4: Selected COSY, HMBC, and NOE correlations for compound **4**.

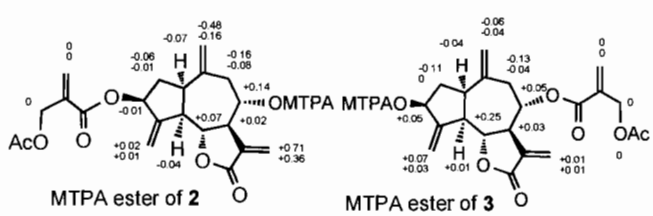

Figure 5: Δδ values detected for MTPA esters of compound **2** and **3** (measured in acetone-d_6 for **2** and $CDCl_3$ for **3**).

The absolute configuration was determined as follows. Compounds **2** and **3** were converted to (*R*)- and (*S*)-MTPA esters [17], respectively, and the chemical shift differences were measured. The results were shown in Figure 5. The absolute configuration of compounds **2** and **3** were established as 1*R*, 3*S*, 5*R*, 6*R*, 7*R*, 8*S*. Similar results were also reported by Wang et al [16].

Compound **5** was isolated from the root extract, but not from the leaves. This compound exhibited a quasi molecular ion peak at *m/z* 261 and the molecular formula was determined to be $C_{17}H_{24}O_2$. The COSY and HMBC correlations were shown in Figure 6. The fragmentations in the mass spectrum suggested that two triple bonds connected to the epoxide moiety (Figure 6). The relative and absolute configurations were not determined due to a minute amount of the material.

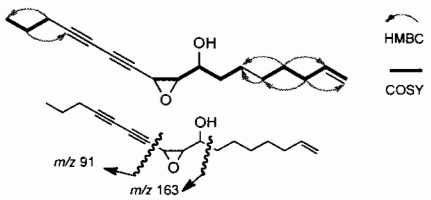

Figure 6: Selected COSY and HMBC correlations as well as MS fragmentation for compound **5**.

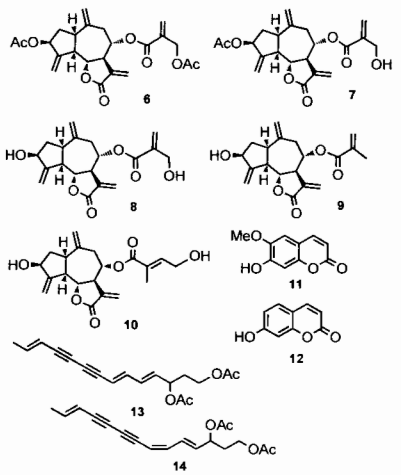

Figure 7: Known compounds isolated in this plant.

The other compounds isolated were known and they were identified as cynaropicrin diacetate (**6**) [15], cynaropicrin monoacetate (**7**) [18], cynaropicrin (**8**) [15, 19-21], **9** [22], **10** [23], scopoletin (**11**) [24], umbelliferone (**12**) [25], **13** [26], and **14** [26] (Figure 7). Although desacetyl derivatives of **1-3** are known [27], they have not been isolated from this extract.

Experimental

Specific rotations and CD spectra were measured on a JASCO P-1030 and a JASCO J-725 auto recording polarimeter; IR spectra, on a SHIMADZU FT/IR-8400S spectrophotometer; ^1H and ^{13}C NMR spectra, on a Varian 500MR (500 MHz and 125 MHz, respectively) spectrometer. Mass spectra, including high-resolution ones, were recorded on a JEOL JMS-700 MStation. Chemcopak Nucleosil 50-5 (4.6×250 mm) with a solvent system of hexane-ethyl acetate was used for HPLC (JASCO pump system). Silica gel BW-127ZH (100-270 mesh, Fuji Sylisia) was used for column chromatography. Silica gel 60 F_{254} plates (Merck) were used for TLC.

The leaves of *S. katochaete*, collected in Sangdui, Sichuan (4001 m) in 2009 (voucher specimen, No. 0927, was deposited in the Herbarium of Kunming Institute of Botany and was identified by Dr. Takayuki Kawahara, Hokkaido Research Center, Forestry and Forest Products Research Institute, Incorporated Administrative Agency, Japan) was extracted with EtOAc to give an extract (1.4 g), which was separated by a silica-gel column chromatography (hexane:AcOEt, in gradient) followed by HPLC (Nucleosil 50-5, hexane:AcOEt) to isolate **1** (3.6 mg), **2** (13.1 mg), **3** (11.8 mg), and **4** (2.7 mg) as well as cynaropicrin diacetate (**6**) (6.9 mg), cynaropicrin monoacetate (**7**) (5 mg), cynaropicrin (**8**) (12.6 mg), **9** (1.8 mg), **10** (7.3 mg), scopoletin (**11**) (53.4 mg), and 7-hydroxy-coumarin (**12**) (106.2 mg). From the root extracts (219.9 mg), **5** (0.8 mg), and a mixture of **13** and **14** (2.8 mg) was isolated.

Compound (**1**)
$[\alpha]_D$: +65.3 (c 0.36, EtOH).
FTIR (KBr): 1769, 1745, 1726, 1643 cm^{-1}.
MS (CI): *m/z* 515 $[M+H]^+$, 455, 387, 371, 227 (base), 127.
HRMS (CI): Obs *m/z* 515.1924 $[M+H]^+$ (Calcd for $C_{27}H_{31}O_{10}$ 515.1917).

Compound (**2**)
$[\alpha]_D$: +74.4 (c 0.63, EtOH).
FTIR (KBr): 3502, 1765, 1745, 1726, 1641 cm^{-1}.
MS (CI): *m/z* 389 $[M+H]^+$, 329, 261, 245 (base), 227, 131, 127.
HRMS (CI) Obs *m/z* 389.1595 $[M+H]^+$ (Calcd for $C_{21}H_{25}O_7$ 389.1601).

Compound (**3**)
$[\alpha]_D$: +133.7 (c 0.11, EtOH).
FTIR (KBr): 3443, 1765, 1745, 1726, 1641 cm^{-1}.
MS (CI): *m/z* 388 $[M]^+$, 245, 244, 227 (base), 127.
HRMS (CI): Obs *m/z* 388.1513 $[M]^+$ (Calcd for $C_{21}H_{24}O_7$ 388.1522).
CD [θ] 204.2 nm, +58084 (EtOH).

Compound (**4**)
$[\alpha]_D$: +70.1 (c 0.13, EtOH).
FTIR (KBr) 3470, 1765, 1728, 1643 cm^{-1}.
MS (CI) *m/z* 473 $[M+H]^+$, 413, 329, 245, 227 (base), 127.
HRMS (CI) Obs *m/z* 473.1798 $[M+H]^+$ (Calcd for $C_{25}H_{29}O_9$ 473.1811).

Compound (**5**)
$[\alpha]_D$: -39.9 (c 0.08, EtOH).
FTIR (KBr): 3393, 2253, 1639, 910 cm^{-1}.
^1H NMR (500 MHz, C_6D_6): 5.76 (1H, ddt, J = 17.1, 10.3, 6.8 Hz, H-2), 5.03 (1H, ddt, J = 17.1, 2.2, 1.4 Hz, H-1), 4.99 (1H, ddt, J = 10.3, 2.2, 1.4 Hz, H-1), 3.57-3.63 (1H, m, H-8), 3.06 (1H, d, J = 3.8 Hz, H-10), 2.59 (1H, dd, J = 7.7, 3.8 Hz, H-9), 1.93 (2H, qt, J = 6.8, 1.4 Hz, H-3), 1.76 (2H, t, J = 7.2 Hz, H-15), 1.61-1.54 (1H, m, H-7), 1.50-1.42 (1H, m, H-7), 1.41-1.32 (1H, m, H-6), 1.25 (2H, quint, J = 6.8 Hz, H-4), 1.23-1.16 (1H, m, H-6), 1.19-1.11 (2H, m, H-5), 1.15 (2H, sext, J = 7.2 Hz, H-16), 0.68 (3H, t, J = 7.2 Hz, H-17).
^{13}C NMR (125 MHz, C_6D_6): 139.2 (CH, C-2), 114.5 (CH_2, C-1), 81.8 (C, C-14)*, 71.5 (C, C-13)*, 71.4 (C, C-12)*, 70.5 (CH, C-8), 65.6 (C, C-11)*, 60.9 (CH, C-9), 44.6 (CH, C-10), 35.1 (CH_2, C-7), 34.1 (CH_2, C-3), 29.4 (CH_2, C-5), 29.2 (CH_2, C-4), 25.1 (CH_2, C-6), 21.7 (CH_2, C-16), 21.1 (CH_2, C-15), 13.3 (CH_3, C-17). (* may be interchanged).
MS (CI): *m/z* 261 $[M+H]^+$, 163, 135 (base), 109, 91, 79.
HRMS (CI): Obs *m/z* 261.1848 $[M+H]^+$ (Calcd for $C_{17}H_{25}O_2$ 261.1855).

Acknowledgments - This work is dedicated to the memory of the late Professor Emeritus of the University of Tokyo, Takeyoshi Takahashi (1926-2010). We thank Mrs. Guowen Hu of Kunming Institute of Botany for research coordination. Identification of the plant was carried out by Dr. Takayuki Kawahara, Hokkaido Research Center, Forestry and Forest Products Research Institute, Incorporated Administrative Agency, which was deeply appreciated. This work was partly supported by a Grant-in-Aid for Scientific Research from JSPS (No. 21404009).

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