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Sinodielides E—H, four New Guaianolides, from the Root of *Sinodielsia yunnanensis*

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Four new guaianolides, sinodielides E—H (1—4), were isolated from the root of *Sinodielsia yunnanensis* Wolff. Their structures were established by spectral evidence.

Key words *Sinodielsia yunnanensis*; Umbelliferae; guaianolide; sinodielide E; sinodielide F; sinodielide G

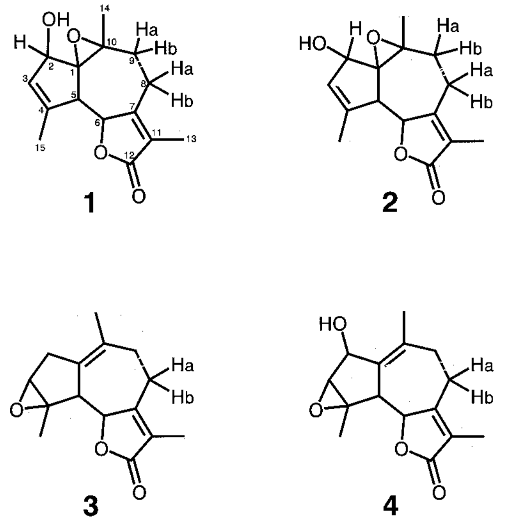
The root of *Sinodielsia yunnanensis* Wolff, "huang gao ben," is a Chinese folk medicine used as an antipyretic, analgesic, and diaphoretic agent in local areas of Yunnan province, China.[1)] In the course of our studies on the phenolic components of Umbelliferous plants, we investigated the constituents of this medicinal plant, and isolated four new guaianolides, sinodielides A—D, together with bergapten, scopoletin and falcarindiol.[2)] The continuing search led us to isolate four new guaianolides, sinodielides E—H (**1**—**4**). This paper deals with the structural elucidation of **1**—**4**.

The ethanolic root extract of *S. yunnaensis* was subjected to a combination of silica gel and Sephadex LH-20 chromatography in the various solvent systems to afford four new guaianolides, sinodielides E—H (**1**—**4**).

Compound **1**, colorless needles, mp 163.6—164.0 °C, $[\alpha]_D$ +46.3° (c=0.549, $CHCl_3$), was assigned the molecular formula $C_{15}H_{18}O_4$ ($[M]^+$ m/z 262.1197) by high resolution electron impact (HR-EI)-MS. The UV spectrum showed absorption maxima at 217 nm and IR spectrum absorption bands at 3191, 1763, 1670 and 1444 cm^{-1}, suggesting unsaturated lactone ring. The ^1H-NMR spectrum (Table 1) showed signals assignable to an olefinic methine proton [δ 5.77 (1H, qm, J=1.8 Hz)], two adjacent methine protons [δ 4.71 (1H, dq, J=11.0, 1.4 Hz), 2.55 (1H, dq, J=11.0, 1.4 Hz)], two adjacent methylene protons [δ 2.68 (1H, ddd, J=14.0, 5.3, 2.3 Hz), 2.44 (1H, br t, J=14.0 Hz) and 2.24 (1H, ddd, J=14.9, 5.3, 3.1 Hz), 1.98 (1H, ddd, J=14.9, 14.0, 2.3 Hz)], and a methyl group [δ 1.51 (3H, br s)]. These signals were closely related to those of sinodielide D (**5**), except for the presence of a signal due to a methine proton attached to an oxygen atom [δ 4.53 (1H, br d, J=8.0 Hz)] instead of the signal due to a methylene proton at C-2. The ^{13}C-NMR spectrum of **1** (Table 2) was also related to that of **5** except for the presence of a methine carbon signal at δ 71.70 and the lack of a methylene carbon signal at δ 37.55. Thus, **1** was assumed to be 2-hydroxy sinodielide D, and this presumption was confirmed by observation of the long-range correlation of a hydroxy group and C-1 in the heteronuclear multiple-bond coherence (HMBC) spectrum of **1** (Fig. 1).

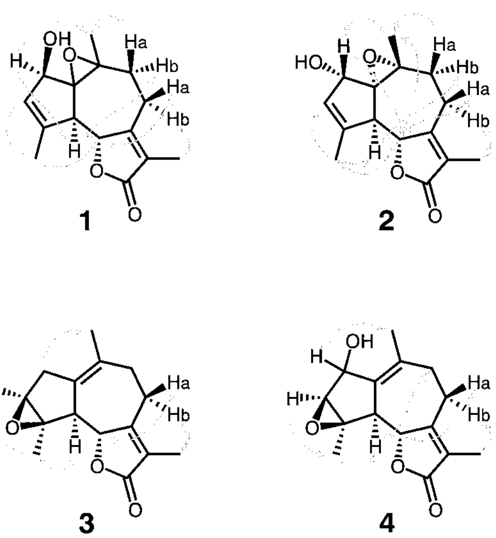
The relative stereostructure, except for an epoxy ring of **1**, was estimated on the basis of the analysis of its nuclear Overhauser effect spectroscopy (NOESY), as described for **1** (Fig. 2), although the absolute stereochemistry remains to be determined.

Compound **2**, colorless needles, mp 102.8—103.0 °C, $[\alpha]_D$ −168.7° (c=0.435, $CHCl_3$), was assigned the molecular formula $C_{15}H_{18}O_4$ ($[M]^+$ m/z 262.1197), the same as **1**, by HR-EI-MS. In the ^1H-NMR spectrum of **2** (Table 1), the signals due to an olefinic methine proton [δ 5.75 (1H, qm, J=0.7 Hz)], a methine proton [δ 4.72 (1H, br s)], a set of adjacent methine protons [δ 4.54 (1H, dq, J=11.3, 0.8 Hz), 2.42 (1H, dq, J=11.3, 0.7 Hz)], two methylene protons [δ 2.87 (1H, ddd, J=15.3, 7.1, 1.6 Hz) and 2.32 (1H, m), 2.32



1 **2** **3** **4**

Fig. 1. The Main HMBC Correlations of **1**—**4**



1 **2** **3** **4**

Fig. 2. NOE Correlations of **1**—**4**

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Table 1. ^{1}H-NMR Data for Compounds **1**—**4** in $CDCl_3$

	1	**2**	**3**	**4**
2	4.53 br d (8.0)	4.72 br s	2.07 m	4.68 br d (9.8)
3	5.77 qm (1.8)	5.75 qm (0.7)	3.39 d (2.3)	3.57 d (2.5)
5	2.55 dq (11.0, 1.4)	2.42 dq (11.3, 0.7)	2.51 br d (10.1)	2.46 dd (10.3, 1.8)
6	4.71 dq (11.0, 1.4)	4.54 dq (11.3, 0.8)	4.73 dd (10.1, 1.6)	4.73 dd (10.3, 1.6)
8	2.68 ddd (14.0, 5.3, 2.3)	2.87 ddd (15.3, 7.1, 1.6)	2.80 m	2.83 m
	2.44 br t (14.0)	2.32 m	2.07 m	2.21 m
9	2.24 ddd (14.9, 5.3, 3.1)	2.32 m	2.66 dd (18.1, 1.4)	2.21 m
	1.98 ddd (14.9, 14.0, 2.3)	1.56 m	2.52 dm (18.1)	
13	1.83 dd (1.4, 1.4)	1.83 dm (1.6)	1.83 dm (1.4)	1.84 dm (1.6)
14	1.51 br s	1.54 d (0.5)	1.71 br d (1.6)	1.93 dd (1.8, 0.9)
15	2.03 d (1.4)	1.99 dm (0.7)	1.64 s	1.64 s
–OH	2.37 d (8.0)			

Chemical shifts are δ values and are followed by multiplicities and J values (in Hz).

Table 2. ^{13}C-NMR Data for Compounds **1**—**4** in $CDCl_3$

	1	**2**	**3**	**4**
1	71.07	71.60	133.76	135.65
2	71.70	72.29	31.88	72.12
3	130.99	130.96	65.14	68.06
4	142.33	143.54	68.17	67.81
5	50.51	55.74	51.74	51.44
6	82.42	84.51	81.19	81.14
7	162.35	161.01	163.87	163.19
8	22.05	22.97	26.44	26.24
9	31.34	34.45	34.04	32.36
10	62.70	64.10	134.82	142.86
11	123.04	123.03	121.48	121.92
12	174.07	173.48	174.12	173.86
13	8.39	8.43	8.27	8.32
14	20.08	17.80	22.55	21.53
15	18.30	18.04	18.92	18.76

(1H, m), and 1.56 (1H, m)], two olefinic methyl group [δ 1.99 (3H, dm, J=0.7 Hz), 1.83 (3H, dm, J=1.6 Hz)], and a methyl group [δ 1.54 (3H, d, J=0.5 Hz)] were observed. These signals were closely related to those of **1**.

These findings indicated that **2** is a stereoisomer of **1**. To determine the structure of **2**, measurements of H–H correlation spectroscopy (H–H COSY), heteronuclear multiple-quantum coherence (HMQC), and HMBC spectra were carried out. The relative structure of **2** was deduced by the results of NOE experiments (Fig. 2). No NOE was observed between H-2/H-5, in contrast to that of **1**, in which a correlation between H-2/H-6 was observed, indicating that **2** is a stereoisomer which differed from **1** in the configuration at the C-2 position.

Compound **3**, a colorless amorphous powder, $[\alpha]_D$ +6.1° (c=0.405, $CHCl_3$), was assigned the molecular formula $C_{15}H_{18}O_3$ ($[M]^+$ m/z 246.1245) by HR-EI-MS. The ^{1}H-NMR spectrum of **3** (Table 1) showed signals due to an adjacent methine proton [δ 4.73 (1H, dd, J=10.1, 1.6 Hz)], two methylene protons [δ 2.08 (1H, m) and 2.07 (1H, m), 2.66 (1H, dd, J=18.1, 1.4 Hz) and 2.52 (1H, dm, J=18.1 Hz)], and two olefinic methyl groups [δ 1.83 (3H, dm, J=1.4 Hz), 1.71 (3H, br d, J=1.6 Hz)]. These signals are similar to those of sinodielide B (**6**) except for the observation of a higher field shift of C-2 and C-3 at δ 2.51 (1H, br d, J=10.1 Hz) and 3.39 (1H, d, J=2.3 Hz), and a C-15 methyl proton at δ 1.64 (3H, s). On the other hand, the ^{13}C-NMR spectrum of **3** (Table 2) is closely related to that of **6**, except for the disappearance of a C-3 methine carbon and a C-15 methyl carbon linked to C-4, and the appearance of two carbons, a methine carbon and a quaternary carbon, attached to an oxygen atom at δ 68.17 and 65.14.

These findings indicated that **3** is a compound constructed of an epoxy ring at C-3/C-4 of **6**. To confirm this structure, extensive two dimensional (2D)-NMR experiments (H–H COSY, HMQC, and HMBC) were carried out. The relative configuration of an epoxy ring was assumed from the observation of NOE correlation between H-5/H-15 and H-15/H-3 in the NOESY spectrum of **3** (Fig. 2).

Compound **4**, a pale yellow viscous oil, $[\alpha]_D$ −7.3° (c=0.379, $CHCl_3$), was assigned the molecular formula $C_{15}H_{18}O_4$ ($[M]^+$ m/z 262.1195) by HR-EI-MS. The ^{1}H-NMR spectrum of **4** (Table 1) exhibited the presence of adjacent methine protons [δ 4.73 (1H, dd, J=10.3, 1.6 Hz), 2.46 (1H, dd, J=10.3, 1.8 Hz)], a methine proton [δ 3.57 (1H, d, J=2.5 Hz)], two methylene protons [δ 2.83 (1H, m), and 2.21 (1H, m), 2.21 (2H, m)], two olefinic methyl groups [δ 1.93 (3H, dd, J=1.8, 0.9 Hz), 1.84 (3H, d, J=1.6 Hz)], and a methyl group [δ 1.64 (3H, s)]. These signal patterns were similar to those of **3**, except for the lack of a signal assignable to the methylene proton at C-2 and the presence of a methine proton linked to an oxygen atom [δ 4.68 (1H, br d, J=9.8 Hz)]. The ^{13}C-NMR spectrum (Table 2) showed a methine carbon signal attached to an oxygen atom at δ 72.12, instead of the methylene carbon signal at C-2, suggesting that **4** is the structure which bears a hydroxy group at the C-2 position of **3**. This structure was confirmed by the analyses of 2D-NMR experiments (H–H COSY, HMQC, and HMBC).

The relative configuration, except for the C-2 position, was assumed by the results of the NOESY spectrum of **4**, as shown in Fig. 2.

The isolation of the guaianolides from the umbrlliferaus plants had hardly ever been reported. The biological activities of sinodielides A—H are still under investigation.

Experiments

General ^{1}H- and ^{13}C-NMR, distortionless enhancement by polarization transfer (DEPT), HMQC, and HMBC spectra were recorded on a Varian UNITY INOVA-500 spectrometer, operating at 500 MHz for proton and 125 MHz for carbon, with tetramethylsilane (TMS) as an internal standard. HR-EI-MS spectra were obtained using a Hitachi M-4100H (70 eV) mass spectrometer. UV and IR spectra were recorded on a Shimadzu UV-2100 and a Perkin Elmer FT-IR 1720 spectrophotometer, respectively. Optical rotatory dispersion (ORD) spectra were recorded on a JASCO J820 digital polarimeter. Column chromatography was performed using Merck Silica gel F_{254} plates (0.25 mm) and Sephadex LH-20. Spots and bands were detected by UV irradiation (254 and 365 nm).

Plant Material Air-dried roots of *S. yunnaensis* (5 kg) were collected from plants grown in Lijiang, Yunnan Province, China, in September 1999. A voucher specimen is deposited in the Institute of Botany, Jiangsu Province, and Academia Sinica, Nanjing, China. The plant was identified by one of the authors (N.W.).

Extraction and Isolation The roots were chopped into small pieces and extracted with EtOH (10 l×5) under reflux. The combined EtOH extracts were concentrated to dryness *in vacuo*. The residue (626.4 g) was subjected to column chromatography on silica gel (4.5 kg), and eluted successively with a hexane–EtOAc solvent system with increasing polarity (5 : 1→1 : 2) to afford 18 fractions (fr.) [fr. 1 (91.5 g), fr. 2 (78.4 g), fr. 3 (156.6 g), fr. 4 (7.7 g), fr. 5 (5.7 g), fr. 6 (6.5 g), fr. 7 (2.7 g), fr. 8 (3.6 g), fr. 9 (6.1 g), fr. 10 (6.5 g), fr. 11 (8.2 g), fr. 12 (12.4 g), fr. 13 (7.7 g), fr. 14 (12.8 g), fr. 15 (14.3 g), fr. 16 (28.2 g), fr. 17 (54.7 g), and fr. 18 (38.9 g). Fraction 2 was rechromatographed on silica gel with hexane–EtOAc (3 : 1) followed by Sephadex LH-20 to give **1** (66 mg), **2** (105 mg), **3** (23 mg), and **4** (7 mg).

Sinodielide E (**1**): Colorless needles, mp 163.6—164.0 °C, HR-EI-MS: *m/z* 262.1197 $[M]^+$ (Calcd for $C_{15}H_{18}O_4$: 262.1204). $[\alpha]_D^{22}$ +46.3° (c=0.549, $CHCl_3$), IR (KBr) cm^{-1}: 3191, 1763, 1670, 1444. UV λ_{max} (MeOH) nm (log ε): 217.0 (4.04). ^1H- and ^{13}C-NMR data are shown in Tables 1 and 2.

Sinodielide F (**2**): Colorless needles, mp 102.8—103.0 °C, HR-EI-MS: *m/z* 262.1197 $[M]^+$ (Calcd for $C_{15}H_{18}O_4$: 262.1204). $[\alpha]_D^{22}$ −168.7° (c=0.435, $CHCl_3$), IR (KBr) cm^{-1}: 3248, 1763, 1673, 1438. UV λ_{max} (MeOH) nm (log ε): 220.0 (3.86). ^1H- and ^{13}C-NMR data are shown in Tables 1 and 2.

Sinodielide G (**3**): Colorless amorphous powder, HR-EI-MS: *m/z* 246.1245 $[M]^+$ (Calcd for $C_{15}H_{18}O_3$: 246.1255). $[\alpha]_D^{22}$ +6.1° (c=0.405, $CHCl_3$), IR (KBr) cm^{-1}: 1757, 1672, 1445. UV λ_{max} (MeOH) nm (log ε): 206.0 (3.92). ^1H- and ^{13}C-NMR data are shown in Tables 1 and 2.

Sinodielide H (**4**): Pale yellow viscous oil, HR-EI-MS: *m/z* 262.1195 $[M]^+$ (Calcd for $C_{15}H_{18}O_4$: 262.1204). $[\alpha]_D^{22}$ −7.3° (c=0.379, $CHCl_3$), IR (KBr) cm^{-1}: 3449, 1752, 1639, 1477. UV λ_{max} (MeOH) nm (log ε): 291.0 sh (2.93), 210.0 (3.97). ^1H- and ^{13}C-NMR data are shown in Tables 1 and 2.

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