

## Neoclerodane Diterpenoids from *Ajuga taiwanensis*

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**Phytochemical investigation of *Ajuga taiwanensis* resulted in the isolation of seven neoclerodane diterpenes, four of which ajugalide-A (1), -B (2), -C (3), and -D (4), are new and the remaining three are known diterpenes, ajugamacrin B (5), ajugapantins A (6), and ajugamarin C1 (7). Their structures were elucidated in spectral and chemical transformation studies.**

**Key words** *Ajuga taiwanensis*; Labiatae; diterpene

*Ajuga taiwanensis* NAKAI ex MURATA belongs to genus *Ajuga* (Labiatae) and is mainly distributed in Taiwan, the Philippines, and Ryukyus. Various species of *Ajuga* have been used for the treatment of incised wounds, snakebite, abdominal pain, fever, sore throat, cold, and lung disease in Taiwanese folk medicine.<sup>1)</sup> Species of *Ajuga* have been reported to contain various bioactive clerodane diterpenoids,<sup>2–4)</sup> phytoecdysteroids,<sup>5–7)</sup> and iridoids.<sup>8–10)</sup> *A. taiwanensis* is often used for the treatment of hepatitis and hepatoma in Taiwanese folk medicine. In continuing chemical studies on medicinal plants of Taiwan, we investigated the constituents of this plant, which resulted in the isolation of seven neo-clerodane diterpenoids. We report here the isolation and structural elucidation of four new neoclerodane diterpenes, ajugalide-A, -B, -C, and -D, using spectroscopic methods and in chemical transformation studies.

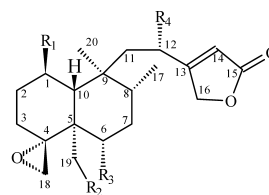
### Results and Discussion

Ajugalide-A (**1**) was isolated as an optically active, white amorphous solid, mp 205–206 °C. The high-resolution fast-atom bombardment mass spectrum (HR-FAB-MS) of **1** showed a *pseudo* molecular ion peak ( $[M+H]^+$ ) at  $m/z$  509.2389, which is in agreement with the molecular formula  $C_{26}H_{36}O_{10}$ . Its  $^1H$ - and  $^{13}C$ -NMR spectra were closely related to those of known compounds **6** and **7**, suggesting that **1** has a neo-clerodane structure corresponding to that of **6** except for the positions of four substituted groups, one hydroxyl group, and three acetyls. To confirm the structure of **1**, two-dimensional correlation spectroscopy (2D-COSY) and the long-range  $^{13}C$ - $^1H$  correlation in heteronuclear multiple bond correlation (HMBC) experiments were conducted. The  $^3J$  HMBC correlation of H-12 at  $\delta$  5.80 with the carbon signal at  $\delta$  169.5 and of the H-6 signal at  $\delta$  4.68 with carbon resonance at  $\delta$  169.9 established the locations of two acetate groups at C-6 and C-12, respectively. By comparing the chemical shift of H-1 in compound **1** with those of known compounds **6** and **7**, a hydroxyl group was placed at C-1 and hence the other acetate group was attached to C-19. Acetylation of **1** yielded a product that was identical in spectral data to ajugapantins A (**6**). Thus compound **1** was identified as a 1-deacetyl derivative of ajugapantins A (**6**).<sup>11)</sup> On the basis of the above data, the absolute structure of **1** was established to be (12*S*)-6 $\alpha$ ,12,19-triacetoxy-1 $\beta$ -hydroxy-4,18-epoxyneoclerod-13(14)-en-15,16-olide.

Ajugalide-B (**2**) was obtained as an optically active, white amorphous solid. The HR-FAB-MS established the molecular formula for **2** to be  $C_{26}H_{36}O_{10}$ , indicating it to be an iso-

mer of **1**. Comparison of the  $^1H$ - and  $^{13}C$ -NMR spectral data of **2** with those of **1** revealed the same relative arrangements of carbons and protons except for H-12 and H-1, and C-12 and C-1. The resonances corresponding to H-1 and H-12 were shifted to  $\delta$  5.68 and  $\delta$  4.72 in **2** from  $\delta$  4.32 and  $\delta$  5.80 in **1**, respectively. Similarly, in comparing **1** with **2**, the chemical shifts were changed for C-1 and C-12 by +3.0 and -3.4 ppm, respectively. These suggest that an acetate group in **2** was located at C-1, and thus a hydroxyl group at C-12. To confirm the proposed structure, COSY, HMQC, and HMBC experiments were conducted. Acetylation of **2** with acetic anhydride and pyridine at room temperature also gave ajugapantins A (**6**).<sup>11)</sup> Thus **2** was defined as (12*S*)-1 $\beta$ ,6 $\alpha$ ,19-triacetoxy-12-hydroxy-4,18-epoxyneoclerod-13(14)-en-15,16-olide.

Ajugalide-C (**3**), an optically active, white amorphous solid, exhibited an  $[M+H]^+$  ion peak at  $m/z$  451, corresponding to the molecular formula  $C_{24}H_{34}O_8$ . The  $^1H$ - and  $^{13}C$ -NMR spectra (Tables 1, 2) resembled those of **1** and **2** except for H-1 and C-1 signals, indicating that the structural difference resided only in the A-ring of the neoclerodane skeleton. The absence of the 1-hydroxyl function was evidenced by the disappearance of a ddd signal corresponding to H-1 $\alpha$  [**2** at  $\delta$  5.68 (1H, ddd,  $J=10.8, 10.8, 4.8$  Hz)], existence of two multipliers for H-1, and the change in the H-10 signal from the doublet to a doublet of a doublet. This was further confirmed



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
<b>1</b>	OH	OAc	OAc	OAc
<b>2</b>	OAc	OAc	OAc	OH
<b>3</b>	H	OAc	OAc	OH
<b>5</b>	OAc	OAc	OAc	OCOCH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>
<b>6</b>	OAc	OAc	OAc	OAc
<b>7</b>	OH	OAc	OAc	OH

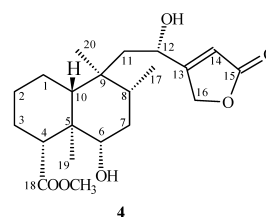


Table 1. <sup>1</sup>H-NMR Spectral Data<sup>a)</sup> of Compounds **1**—**4**, **6** and **7**

	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>6</b>	<b>7</b>
1	4.32 ddd (10.4, 10.4, 4.8)	5.68 ddd (10.8, 10.8, 4.8)	1.70—1.50 1.26 m	1.80—1.50 1.47 m	5.50 ddd (10.8, 10.8, 4.4)	4.37 br dd (10.6, 10.6)
2	2.20 dddd (12.8, 4.8, 4.8, 2.0, $\alpha$ ) 1.70—1.40 ( $\beta$ )	2.23 br d (10.8, $\alpha$ ) 1.63—1.56 ( $\beta$ )	1.70—1.50	1.80—1.50	2.21 dddd (12.8, 4.8, 4.8, 2.4, $\alpha$ ) 1.80—1.40 ( $\beta$ )	2.20 br d (12.8, $\alpha$ ) 1.70—1.55 ( $\beta$ )
3	2.27 dddd (14.0, 14.0, 4.8, 2.0, $\alpha$ ) 1.15 ddd (14.0, 4.8, 2.0, $\beta$ )	2.39 dddd (10.8, 10.8, 4.0, 2.0, $\alpha$ ) 1.15 ddd (10.8, 2.8, 2.8, $\beta$ )	2.14 br dd (12.8, 12.8, $\alpha$ ) 1.05 ddd (12.8, 2.4, 2.4, $\beta$ )	1.84 m ( $\alpha$ ) 1.33 m ( $\beta$ )	2.37 dddd (11.2, 11.2, 4.8, 2.8, $\alpha$ ) 1.13 ddd (11.2, 4.8, 2.4, $\beta$ )	2.27 br dd (14.0, 14.0, $\alpha$ ) 1.12 br dd (14.0, 4.8, $\beta$ )
4				2.16 dd (12.4, 3.2)		
6	4.68 dd (11.4, 4.6)	4.75 dd (11.6, 4.8)	4.76 m	3.54 dd (11.2, 4.4)	4.68 dd (10.8, 4.0)	4.72 dd (12.4, 4.7)
7	1.70—1.40	1.70 ddd (11.2, 11.2, 4.8, $\alpha$ ) 1.63—1.56 ( $\beta$ )	1.70—1.50	1.80—1.50	1.80—1.40	1.70 ddd (12.4, 12.4, 12.4, $\alpha$ ) 1.56 ddd (12.4, 4.7, 4.7, $\beta$ )
8	1.70—1.40 ( $\beta$ )	1.88 m ( $\beta$ )	1.70—1.50	1.80—1.50	1.80—1.40 ( $\beta$ )	1.83 m
10	1.70—1.40	2.54 d (10.8)	1.93 dd (10.4, 2.0)	1.38 dd (10.8, 1.6)	2.15 d (10.8)	2.16 d (10.6)
11	2.52 dd (16.0, 9.6)	2.02 dd (17.2, 11.2)	1.95 dd (15.6, 11.2)	1.88 dd (15.6, 8.8)	2.52 dd (16.0, 8.0)	2.65 dd (15.9, 10.4)
	1.82 d (16.0)	1.72 d (17.2)	1.45 d (15.6)	1.45 d (15.6)	1.80—1.40	1.59 d (15.9)
12	5.80 br d (9.6)	4.72 br d (11.2)	4.77 br d (11.2)	4.74 br d (8.8)	5.85 br d (6.0)	4.73 br d (10.4)
14	5.89 t (1.8)	5.94 t (1.6)	5.95 t (1.3)	5.94 t (2.0)	5.96 t (1.6)	5.87 t (1.6)
16	4.80 dd (17.8, 1.8) 4.73 dd (17.8, 1.8)	4.85 d (1.6)	4.84 d (1.3)	4.89 dd (17.8, 2.0) 4.83 dd (17.8, 2.0)	4.84 dd (16.0, 1.6) 4.75 dd (16.0, 1.6)	4.86 dd (1.6)
17	0.91 d (6.4)	0.86 d (6.4)	0.82 d (6.0)	0.82 d (6.8)	0.83 d (6.0)	0.85 d (6.6)
18	2.98 dd (3.6, 2.0) 2.26 d (3.6)	3.07 dd (3.6, 2.4) 2.32 d (3.6)	2.97 dd (4.0, 2.3) 2.21 d (4.0)		3.02 dd (4.0, 1.2) 2.29 d (4.0)	3.01 dd (3.8, 2.0) 2.27 d (3.8)
19	4.88 d (12.4) 4.31 d (12.4)	4.90 d (12.8) 4.41 d (12.8)	4.84 d (12.0) 4.39 d (12.0)	1.11 s	4.93 d (12.8) 4.37 d (12.8)	4.87 d (12.6) 4.32 d (12.6)
20	0.89 s	0.83 s	0.75 s	0.74 s	0.75 s	0.92 s
Ac	2.13 s 2.10 s 1.95 s	2.14 s 2.09 s 1.96 s	2.11 s 1.96 s		2.13 s 2.11 s 2.07 s 1.95 s	2.10 s 1.95 s
OH		3.45 br s				
COOCH <sub>3</sub>				3.63 s		

<sup>a)</sup> Spectral data were obtained in CDCl<sub>3</sub> at 400 MHz. Chemical shift are given in  $\delta$  values.

by a new methylene carbon signal instead of the methine carbon assigned at C-1 in **2** and an upfield shift of C-10 by 2 ppm in the <sup>13</sup>C-NMR spectrum. The presence of two acetyl groups was inferred by the <sup>1</sup>H-NMR signals at  $\delta$  2.11 and 1.96 together with carbon signals at  $\delta$  171.0 (s), 170.2 (s), 21.2 (q), and 21.2 (q). By comparing the chemical shift of H-12 and C-12 with those of compounds **1** and **2**, the acetate groups were attached at C-6 and C-19. The complete assignments were established using <sup>1</sup>H-<sup>1</sup>H COSY, HMQC, and HMBC experiments. The absent coupling of H-12 with H-11b and vicinal coupling between H-12 and H-11a are consistent with the staggered conformation with *ca.* 90° and *ca.* 150° dihedral angles between the protons. The NOEs between H-17 and H-12, between H-17 and H-11b, and between H-12 and H-8 $\beta$ , combined with the above conformation, revealed the configuration at C-12 to be as depicted in Fig. 1. Consequently, the structure of ajugalide-C was elucidated to be (12*S*)-6 $\alpha$ ,19-diacetoxy-12-hydroxy-4,18-epoxy-neoclerod-13(14)-en-15,16-olide.

Ajugalide-D (**4**) was obtained as a white amorphous solid, and the molecular formula was determined to be C<sub>21</sub>H<sub>32</sub>O<sub>6</sub> in HR-FAB-MS. The <sup>13</sup>C-NMR spectrum of **4** showed five quaternary carbons, six methines, six methylenes, and four methyls (Table 1). The <sup>1</sup>H-NMR spectrum displayed an  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone group bearing an  $\alpha$ -hydrogen atom at  $\delta$  5.94 (1H, d, *J*=2.0 Hz), 4.89 (1H, dd, *J*=17.8, 2.0 Hz), and

4.83 (1H, dd, *J*=17.8, 2.0 Hz), which was also indicated by the IR bands at 1777 (C=O), 1632 (C=C) cm<sup>-1</sup> and the UV absorption at 212 nm. <sup>1</sup>H- and <sup>13</sup>C-NMR complete assignments made using a combination of <sup>1</sup>H-<sup>1</sup>H COSY, HMQC, and HMBC spectra revealed that **4** possesses a tricyclic neoclerodane structure similar to that of ajugalide-C (**3**), but differed in substitution. The presence of a methyl carboxylate group was evidenced by signals at  $\delta$  3.63 (3H, s) together with <sup>13</sup>C-NMR signals at  $\delta$  176.9 (s) and 51.6 (q). This was placed at C-4 instead of the oxirane ring in **1**—**3** based on a doublet of a doublet at  $\delta$  2.16 assignable to H-4 and its HMBC correlations to C-5 and C-18. An extra methyl group at  $\delta$  1.11 was connected to C-5 as it showed HMBC cross peaks with C-4, C-5, C-6, and C-10. An upfield shift of H-6 to  $\delta$  3.54 and downfield shift of C-6 to  $\delta$  77.9 indicated that C-6 was hydroxylated. The relative stereochemistries of H-4, H-6, and H-10 were also deduced to be in the axial orientation from the 12.4-, 11.2-, and 10.8-Hz coupling constants between H-4 and H-3, H-6 and H-7, and H-10 and H-1, respectively. Moreover, the NOE correlations of H-4 with H-6 and H-10, and of H-8 with H-6 and H-10, indicated the *cis*-configuration. The configuration of H-10 with the methyl group at C-5 was determined to be *trans* due to the absence of a NOE cross peak between H-10 ( $\delta$  1.38) and H-19 ( $\delta$  1.11) in the NOESY experiment. On the other hand, the configuration of methyl groups at C-5 with C-9 was determined

Table 2.  $^{13}\text{C}$ -NMR Spectral Data<sup>a)</sup> of Compounds **1**, **2**, **3**, **4**, **6** and **7**

Compound	1	2	3	4	6	7
1	68.7	71.7	21.6	21.4	70.7	69.0
2	36.9	31.9	32.9	25.6	31.9	36.3
3	30.6	30.3	32.7	25.6	30.5	30.6
4	64.3	64.1	65.1	56.0	64.3	64.3
5	45.6	50.0	45.5	44.4	46.1	45.7
6	71.4	71.4	72.3	77.9	71.4	71.6
7	32.8	32.8	24.7	36.2	32.8	33.0
8	38.5	35.0	35.3	35.7	35.5	35.2
9	39.3	39.3	39.4	39.6	39.2	39.4
10	56.5	50.8	49.0	49.5	50.4	52.2
11	43.3	43.9	43.0	43.8	41.8	43.9
12	68.9	65.5	65.3	65.4	66.5	65.0
13	169.0	173.1	173.0	173.5	168.7	175.2
14	115.8	114.5	114.7	114.5	116.3	113.8
15	172.6	173.7	173.2	172.9	172.6	174.1
16	70.8	71.0	70.6	70.7	70.7	71.2
17	13.8	15.5	15.4	15.7	15.8	15.5
18	48.3	49.2	48.4	176.9	48.8	48.7
19	61.5	62.1	61.7	9.4	61.6	61.7
20	15.6	17.4	17.2	17.4	17.1	17.2
Ac	170.6	170.3	171.0		170.6	170.7
	169.9	169.9	170.2		170.0	170.1
	169.5	167.9	21.2		169.6	21.2
	21.1	22.0	21.2		169.6	21.2
	21.1	21.1			22.0	
	21.1	21.1			21.4	
					21.3	
OCH <sub>3</sub>				51.6		

a) Spectral data were obtained in  $\text{CDCl}_3$  at 100 MHz. Chemical shift are given in  $\delta$  values.

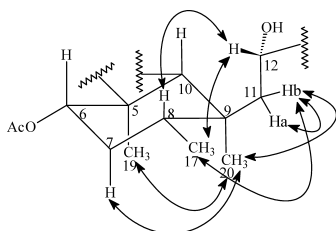


Fig. 1

to be *cis* due to the cross peak between H-19 ( $\delta$  1.11) and H-20 ( $\delta$  0.74) in the NOESY experiment. Based on the above analyses, the structure of ajugalide-D (**4**) is (12*S*)methyl 6 $\alpha$ ,12-dihydroxy-4 $\alpha$ -methoxycarbonyl-18-norneo-clerod-13(14)-en-15,16-olide.

The known compounds ajugamacrin B (**5**),<sup>12)</sup> ajugapantarin A (**6**),<sup>11)</sup> and ajugamarin C1 (**7**)<sup>11)</sup> were identified and characterized by comparison of their spectroscopic data with the value reported in the literature.

#### Experimental

**General** Melting points were determined on a Yanagimoto MP-S3 apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 polarimeter. IR and UV spectra were recorded on Shimadzu FTIR-8501 and Hitachi UV-3210 spectrophotometers, respectively. EIMS was obtained on a VG-70-250S mass spectrometer. The  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR, DEPT, COSY, HMQC, NOESY, and HMBC experiments were recorded on a Bruker AMX-400 spectrometer.

**Plant Material** *A. taiwanensis* was collected from Tainan, Taiwan, in August 2001 and verified by Prof. C.-S. Kuoh. A voucher specimen (TSWu 90003) has been deposited in the Herbarium of National Cheng Kung University, Tainan, Taiwan.

**Extraction and Separation** The dried whole plants of *A. taiwanensis*

(68 g) were extracted with MeOH ( $\times 10$ ) at room temperature and concentrated to give a dark brown syrup (14.7 g). The syrup was partitioned successively between  $\text{H}_2\text{O}$  and  $\text{CHCl}_3$ . The  $\text{CHCl}_3$  layer (3.4 g) was chromatographed directly on silica gel and eluted with a gradient of *n*-hexane and EtOAc to afford 13 fractions. Fractions 6, 7, and 8 were combined, rechromatographed on silica gel, and eluted with  $\text{CHCl}_3$ -MeOH (30:1, v/v) to give **5** (56 mg). Fraction 10 underwent chromatography on silica gel using  $\text{CHCl}_3$ -MeOH (15:1, v/v) as an eluent to afford **1** (2 mg), **2** (5 mg), **3** (1 mg), **4** (0.8 mg), **6** (8 mg), and **7** (11 mg), successively.

**Ajugalide-A (1):** White amorphous solid, mp 205–206 °C.  $[\alpha]_D^{25} -6.2^\circ$  ( $c=0.12$ ,  $\text{CHCl}_3$ ). UV  $\lambda_{\text{max}}$  (MeOH) nm (log  $\epsilon$ ): 212 (3.51). IR (KBr)  $\text{cm}^{-1}$ : 3498, 2970, 2934, 1780, 1743, 1732, 1637, 1449, 1373, 1232, 1161, 1095, 1032, 897, 754.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data, see Tables 1 and 2. FAB-MS  $m/z$ : 509 ( $[\text{M}+\text{H}]^+$ , 49), 466 (6), 450 (4), 449 (12), 391 (4), 329 (10), 311 (14), 201 (28), 185 (100). HR-FAB-MS  $m/z$ : 509.2389 (Calcd for  $\text{C}_{26}\text{H}_{37}\text{O}_{10}$ : 509.2387).

**Preparation of 6 from 1** Acetylation of ajugalide-A (**1**) with  $\text{Ac}_2\text{O}$  and pyridine in the usual manner afforded the 1-acetate **6**, mp 200–202 °C.  $[\alpha]_D^{25} -20.8^\circ$  ( $c=0.04$ ,  $\text{CHCl}_3$ ).

**Ajugalide-B (2):** White amorphous solid, mp 209–210 °C.  $[\alpha]_D^{25} +2.4^\circ$  ( $c=0.27$ ,  $\text{CHCl}_3$ ). UV  $\lambda_{\text{max}}$  (MeOH) nm (log  $\epsilon$ ): 211 (3.3). IR (KBr)  $\text{cm}^{-1}$ : 3520, 2971, 2935, 1779, 1747, 1729, 1714, 1638, 1455, 1373, 1239, 1173, 1137, 1082, 1027, 900, 759.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data, see Tables 1 and 2. EIMS  $m/z$ : 508 ( $[\text{M}]^+$ , 2), 478 (46), 465 (32), 435 (51), 394 (24), 393 (100), 363 (30), 333 (39), 316 (22), 315 (43), 303 (56), 298 (22), 219 (20), 203 (25), 189 (89), 175 (45), 173 (57), 157 (45), 119 (47), 105 (51), 91 (54). HR-FAB-MS  $m/z$ : 509.2389 (Calcd for  $\text{C}_{26}\text{H}_{37}\text{O}_{10}$ : 509.2387).

**Ajugalide-C (3):** White amorphous solid, mp 158–160 °C.  $[\alpha]_D^{25} -10.4^\circ$  ( $c=0.07$ ,  $\text{CHCl}_3$ ). UV  $\lambda_{\text{max}}$  (MeOH) nm (log  $\epsilon$ ): 211 (3.2). IR (KBr)  $\text{cm}^{-1}$ : 3446, 2937, 1776, 1744, 1733, 1637, 1460, 1373, 1250, 1151, 1030, 866, 756.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data, see Tables 1 and 2. FAB-MS  $m/z$ : 451 ( $[\text{M}+\text{H}]^+$ , 11), 436 (2), 408 (2), 391 (4), 331 (9), 203 (14), 180 (88), 135 (100). HR-FAB-MS  $m/z$ : 451.2328 (Calcd for  $\text{C}_{24}\text{H}_{35}\text{O}_8$ : 451.2332).

**Ajugalide-D (4):** White amorphous solid, mp 210–212 °C.  $[\alpha]_D^{25} -12.7^\circ$  ( $c=0.05$ ,  $\text{CHCl}_3$ ). UV  $\lambda_{\text{max}}$  (MeOH) nm (log  $\epsilon$ ): 212 (3.4). IR (KBr)  $\text{cm}^{-1}$ : 3448, 2924, 1777, 1748, 1632, 1461, 1379, 1216, 1149, 1038.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data, see Tables 1 and 2. FAB-MS  $m/z$ : 381 ( $[\text{M}+\text{H}]^+$ , 53), 366 (4),

363 (94), 349 (17), 331 (12), 303 (56), 285 (17), 244 (17), 235 (82), 221 (21), 203 (27), 185 (100). HR-FAB-MS  $m/z$ : 403.2092 (Calcd for  $C_{21}H_{32}O_6Na$ : 403.2097).

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