Two New Quassinoids, Ailantinols A and B, and Related Compounds from *Ailanthus altissima*

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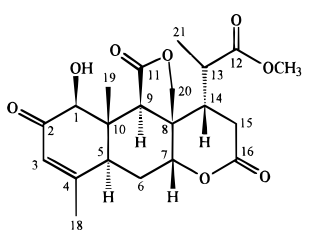
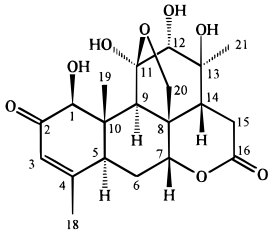
Two new quassinoids, ailantinols A (**1**) and B (**2**), and related compounds were isolated from *Ailanthus altissima*, and their structures were elucidated from spectral evidence.

Many quassinoids with various biological activities such as antitumor, antimalarial, antifeedant, insecticidal, anti-inflammatory, amoebicidal, and herbicidal effects have been isolated from plants in the Simaroubaceae family.[1] Our research has focused on the isolation of biologically active quassinoids from plants such as *Brucea antidysenterica*,[2−8] *Picrasma ailanthoides*,[9−12] and *Brucea javanica*.[13,14] As part of these studies, we investigated the isolation of quassinoids from *Ailanthus altissima* Swingle (= *Ailanthus glandulosa* Desf.) (Simaroubaceae). In this paper, we report the isolation and structural elucidation of two new quassinoids, ailantinols A (**1**) and B (**2**), from *A. altissima*. The known quassinoids, shinjudilactone (**3**),[15,16] ailanthone (**4**),[17,18] shinjulactone A,[19] amaloride,[20,21] amaloride 11-acetate,[20] shinjulactone K,[22] $\Delta^{13(18)}$-dehydroglaucarubinone,[23] $\Delta^{13(18)}$-dehydroglaucarubolone,[24,25] shinjulactone B,[26,27] and shinjulactone C[15,23] also were isolated from this plant; all of these compounds have been reported previously as constituents of *A. altissima*. Compounds **3** and **4** were useful in the structural elucidation of the new compounds **1** and **2**.



1



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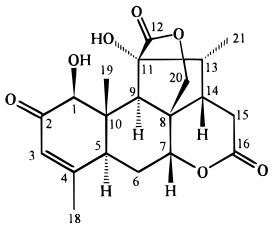

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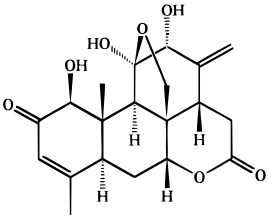

4

Compound **1** was isolated as colorless needles. Its IR spectrum showed the presence of hydroxy (3450 cm^{-1}), γ-lactone (1800 cm^{-1}), δ-lactone (1750 cm^{-1}), ester (1739 cm^{-1}), and α,β-unsaturated carbonyl (1670 cm^{-1}) groups. Its UV spectrum showed an absorption maximum at 235 nm due to a conjugated enone system. Its molecular formula was established as $C_{21}H_{26}O_8$ by HREIMS (*m/z* 406.1597). The ^{1}H- and ^{13}C-NMR spectral data of compound **1** did not coincide with those of any known quassinoid, and we have assigned the name ailantinol A to this new quassinoid.

The ^{1}H-NMR spectrum (Table 1) of **1** was similar to that of **3**, except for the positions of the H-9, H-13, H-14, and OMe signals (δ 3.77, 3.44, 2.82, and 3.60). The former three signals in **1** were shifted downfield by 1.05, 1.26, and 0.54 ppm from the corresponding signals in **3**.

The ^{13}C-NMR spectrum (Table 2) of **1** also was similar to that of **3** except for the positions of some signals in the C-ring and of the OMe signal (δ 52.2). The C-13, C-14, and C-20 signals (δ 36.9, 40.9, and 69.4) in **1** appeared at higher field than those in **3** by 8.7, 12.7, and 6.8 ppm. The C-11 signal (δ 175.6) in **1** shifted to lower field by 96.9 ppm compared with that (δ 78.7) in **3**. DEPT spectra of **1** and **3** showed that the former signal is due to a carbonyl carbon and the latter to a quaternary carbon.

The partial structures of rings A, B, and D in **1** were elucidated from ^{13}C−^{1}H long-range correlations in the HMBC spectrum; most of which are shown by arrows in Figure 1. In addition, the following ^{13}C−^{1}H long-range correlations were also found: the H-9 signal (δ 3.77) with the C-11 signal (δ 175.6), the H-7 signal (δ 4.91) with the C-5 and C-14 signals (δ 40.6 and 40.9), and the H-15α and H-15β methylene signals (δ 3.01 and 2.68) with the C-13 and C-14 signals (δ 36.9 and 40.9). A mass fragment ion peak of *m/z* 151 due to a tropylium ion provided further confirmation of the structure of ring A.

The structure of the cleaved C-ring in **1** was elucidated from the following evidence. In the ^{1}H−^{1}H COSY NMR spectrum, the 13-Me signal (δ 1.31) coupled with the H-13 resonance (δ 3.44), which in turn coupled with the H-14 signal (δ 2.82). The H-14 resonance coupled with the signals (δ 2.68 and 3.01) of the H-15 methylene. In the HMBC spectrum, the ester carbonyl signal (δ

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Table 1. ^{1}H-NMR Spectra[a] of Compounds **1**−**4**

	compound			
proton	**1**[b]	**2**[b]	**3**[c]	**4**[d]
H-1	4.75 s	4.42 s	4.23 s	4.54 s
H-3	6.14 br s	6.12 br s	6.10 br s	6.13 br s
H-5	3.01 m	3.03 br d (13)	3.22 br d (13)	3.07 br d (13)
H-6α	2.35 ddd (15.5, 5, 2.5)	2.19 ddd (15, 3.5, 3)	2.31 ddd (15, 3, 2.5)	2.22 br d (14)
H-6*β*	2.10 ddd (15.5, 13.5, 2.5)	2.07 ddd (15, 3, 3)	2.08 ddd (15, 13, 2.5)	2.05, br dd (14, 13)
H-7	4.91 dd (2.5, 2.5)	4.62 dd (3.5, 3)	4.81 t (2.5)	4.64 br s
H-9	3.77 s	3.37 s	2.72 s	3.53 s
H-12		4.16 br d (5)		4.46 s
H-13	3.44 m		2.18 quin (7)	
H-14	2.82 m	2.55 dd (14.5, 5.5)	2.28 ddd (10.5, 7, 1)	2.83 dd (13, 5)
H-15α	3.01 m	3.29 dd (18.5, 14.5)	3.13 dd (16, 10.5)	3.69 dd (18, 13)
H-15*β*	2.68 dd (17, 5.5)	3.09 dd (18.5, 5.5)	2.70 dd (16, 1)	2.90 dd (18, 5)
H-20α	4.69 d (10.5)	4.78 d (8)	4.79 d (12)	4.11 d (8)
H-20*β*	4.30 d (10.5)	4.14 d (8)	4.31 d (12)	3.66 d (8)
H-21				5.19 br s
				5.28 br s
4-Me	1.77 s	1.76 br s	1.80 br s	1.78 br s
10-Me	1.19 s	1.61 s	1.24 s	1.52 s
13-Me	1.31 d (6.5)	1.67 s	1.24 d (7)	
13-COOMe	3.60 s			
12-OH		7.60 d (5)		*e*

[a] Values are in ppm. The coupling constants (*J* values) in parentheses are in Hz. [b] 500 MHz in C_5D_5N. [c] 400 MHz in C_5D_5N. [d] 400 MHz in C_5D_5N + 2%$CDCl_3$. [e] Not assignable.

Table 2. ^{13}C NMR Spectra[a] of Compounds **1**−**4**

	compound			
carbon	**1**[b]	**2**[b]	**3**[c]	**4**[d]
C-1	84.7 (CH)	84.6 (CH)	83.8 (CH)	84.4 (CH)
C-2	197.5 (C=O)	197.6 (C=O)	196.9 (C=O)	197.3 (C=O)
C-3	126.9 (CH)	126.3 (CH)	126.3 (CH)	126.2 (CH)
C-4	160.3 (C)	162.3 (C)	162.0 (C)	162.1 (C)
C-5	40.6 (CH)	42.6 (CH)	42.2 (CH)	44.8 (CH)
C-6	26.0 (CH_2)	26.1 (CH_2)	27.0 (CH_2)	26.2 (CH_2)
C-7	75.7 (CH)	78.2 (CH)	73.9 (CH)	78.5 (CH)
C-8	45.8 (C)	46.5 (C)	48.4 (C)	45.7 (C)
C-9	54.3 (CH)	44.8 (CH)	55.0 (CH)	48.0 (CH)
C-10	45.0 (C)	45.3 (C)	43.0 (C)	45.5 (C)
C-11	175.6 (C=O)	110.7 (C)	78.7 (C)	110.3 (C)
C-12	172.8 (C=O)	83.0 (C=O)	173.5 (C=O)	80.6 (C=O)
C-13	36.9 (CH)	74.2 (C)	45.6 (CH)	147.4 (C)
C-14	40.9 (CH)	49.0 (CH)	53.6 (CH)	42.5 (CH)
C-15	31.4 (CH_2)	31.8 (CH_2)	32.9 (CH_2)	35.3 (CH_2)
C-16	172.3 (C=O)	170.2 (C=O)	170.6 (C=O)	169.4 (C=O)
C-18	22.2 (Me)	22.4 (Me)	22.1 (Me)	22.5 (Me)
C-19	10.7 (Me)	10.7 (Me)	10.6 (Me)	10.3 (Me)
C-20	69.4 (CH_2)	71.0 (CH_2)	76.2 (CH_2)	72.3 (CH_2)
C-21	10.7 (Me)	26.2 (Me)	13.8 (Me)	118.2 (CH_2)
13-COOMe	52.2 (Me)			

[a] Values are in ppm (C_5D_5N). [b] 125 MHz. [c] 22.5 MHz. [d] 25 MHz.

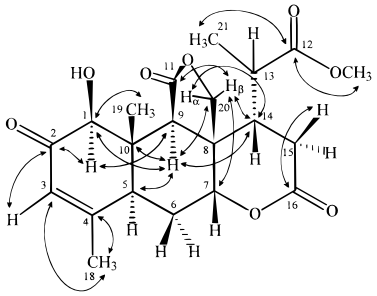

Figure 1. ^{13}C−^{1}H long-range correlations in the HMBC spectrum of **1**.

172.8) showed a ^{13}C−^{1}H long-range correlation with the proton signals (*δ* 1.31 and 3.60) of the 13-Me and the OMe. Furthermore, the C-13 signal (*δ* 36.9) correlated with the H-15*β* and 13-Me signals (*δ* 2.68 and 1.31).

The structure of the *γ*-lactone moiety in **1** was elucidated from the following evidence. In the HMBC NMR spectrum of **1**, the carbon signal (*δ* 175.6, C-11)

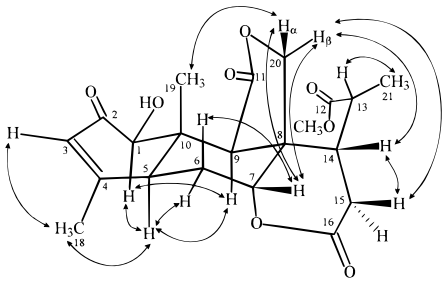

Figure 2. NOE correlations of **1**.

of the *γ*-lactone C=O showed ^{13}C−^{1}H long-range correlation with the H-9 and H-20*β* signals (*δ* 3.77 and 4.30). Furthermore, the H-20 methylene signals (*δ* 4.30 and 4.69) correlated with the C-8 and C-9 signals (*δ* 45.8 and 54.3). These data indicated that the *γ*-lactone moiety bridges C-8 and C-9.

The relative stereochemistry of **1** was confirmed from its NOESY NMR spectrum. The NOE correlations are shown by arrows in Figure 2 and support the proposed structure of **1**.

Compound **2** was obtained as colorless needles. Its IR spectrum showed the presence of hydroxy (3400 cm^{-1}) and *δ*-lactone (1720 cm^{-1}) groups. Its UV spectrum exhibited maximum absorption at 240 nm due to a conjugated enone system. HREIMS (*m*/*z* 394.1624) revealed a molecular formula of $C_{20}H_{26}O_8$, which is 18 units higher than that of **4** ($C_{20}H_{24}O_7$). The spectral data of compound **2** also did not correspond to those of any known quassinoid, and we have assigned the name ailantinol B to this new quassinoid.

The ^{1}H-NMR signals of **2** were similar to those of **4**; however, a methyl signal (*δ* 1.67) in **2** replaced the H-21 exomethylene signals (*δ* 5.19 and 5.28) in **4**. Additionally, the H-12 and H-14 signals (*δ* 4.16 and 2.55) of **2** were shifted upfield by 0.30 and 0.28 ppm, respectively, compared with those of **4**. These findings suggested the presence of a hydroxy group at C-13, which is consistent with the mass spectral data.

The ^{13}C-NMR signals observed for C-1 to C-12 and C-15 to C-20 in **2** were nearly identical with those of **4**.

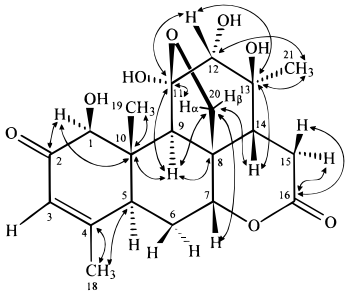

Figure 3. $^{13}C-^{1}H$ long-range correlations in the HMBC spectrum of **2**.

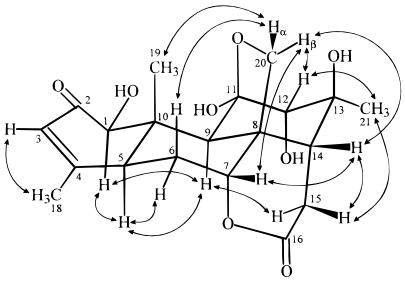

Figure 4. NOE correlations of **2**.

However, in the DEPT NMR spectrum of **2**, C-13 is a quaternary carbon and C-21 is a methyl carbon, whereas these carbons in **4** are both olefinic. The chemical shift value (δ 74.2) of C-13 in **2** is reasonable for a carbon attached to an oxygen atom. From these data, the structure of **2** was proposed as that shown. The $^{13}C-^{1}H$ long-range correlations found in the HMBC spectrum of **2** are depicted by arrows in Figure 3 and are consistent with the proposed structure.

The relative stereochemistry of **2** was confirmed by its NOESY NMR spectrum; the NOE correlations are shown by arrows in Figure 4.

Experimental Section

General Experimental Procedures. Melting points were determined on an MRK air-bath-type melting point apparatus and are uncorrected. Specific rotations were obtained on a JASCO DIP-370 digital polarimeter (l = 0.5 dm). IR and UV spectra were recorded on a JASCO IR-810 spectrometer and Hitachi 320-S spectrometer, respectively. ^{1}H- and ^{13}C-NMR spectra were determined on a Varian VXR-500, a JASCO GSX-500, or a JEOL Alpha-400 spectrometer in C_5D_5N using TMS as an internal standard. MS were recorded on a Hitachi M-80 instrument. Si gel (Merck, type 60, 70−230 mesh) and Sephadex LH-20 (Pharmacia) were used for column chromatography. Precoated Si gel plates (Merck, $60F_{254}$) of 0.25-mm thickness were used for analytical TLC, and plates of 1-mm and 2-mm thickness were used for preparative TLC. Components were detected using a UV lamp (254 and 365 nm). Analytical HPLC was performed on a Tosoh liquid chromatograph equipped with a UV detector (254 nm) and a reversed-phase column (TSK-gel ODS-$80T_s$) using a MeOH/H_2O mixture as solvent. Preparative HPLC was carried out on Tosoh or Gilson liquid chromatographs equiped with a reversed-phase column (Dynamax-60A and/or Lichrosorb RP-18) using the same solvents as employed for analytical HPLC.

Plant Material. In 1982, five trees of *A. altissima* were planted in the Higashisenda campus of Hiroshima University. In 1990, four plants were harvested, and the stem bark was collected for extraction. A voucher specimen was deposited at the above campus.

Extraction and Isolation. The stem bark of *A. altissima* (fresh material, 33 kg) was cut into small pieces and soaked in MeOH (76 L) for 1 year at room temperature. Evaporation of the solvent gave a MeOH extract (2.5 kg), which was partitioned between MeOH/H_2O (2:1) and *n*-hexane. The MeOH/H_2O layer was then extracted with $CHCl_3$ to afford a $CHCl_3$ extract (221 g). Si gel column chromatography of this extract (221 g) with EtOAc/Et_2O (1:1, v/v) (13 L) gave 95 fractions and with MeOH (13 L) gave 27 fractions. Each fraction was checked by analytical TLC and HPLC; combination gave 19 subfractions: 1 (5.94 g), 2 (6.67 g), 3 (4.89 g), 4 (5.53 g), 5 (6.42 g), 6 (6.47 g), 7 (4.35 g), 8 (4.99 g), 9 (4.55 g), 10 (4.02 g), 11 (4.85 g), 12 (3.29 g), 13 (5.83 g), 14 (6.01 g), 15 (15.2 g, MeOH), 16 (16.1 g, MeOH), 17 (15.0 g, MeOH), 18 (19.6 g, MeOH), and 19 (18.7 g, MeOH).

Subfraction 12 (3.29 g) was subjected to preparative TLC (EtOAc/Et_2O, 1:1) to give six fractions: 12-1 (0.28 g), -2 (1.77 g), -3 (1.09 g), -4 (0.35 g), -5 (0.31 g), and -6 (0.36 g). Preparative HPLC (MeOH/H_2O, 2:8) of fraction 12-2 (1.77 g) gave nine additional fractions: 12-2-1 (301 mg), -2 (172 mg), -3 (95 mg), -4 (143 mg), -5 (36 mg), -6 (93 mg), -7 (198 mg), -8 (95 mg), and -9 (55 mg). Repeated preparative HPLC (MeOH/H_2O, 3:7) of fraction 12-2-8 (95 mg) afforded the new quassinoid, ailantinol A (**1**, 15 mg, 0.000 045%), as colorless needles. This compound was also isolated from subfractions 10 and 11; the total amount was 31.0 mg (0.000 95%). Fraction 12-2-6 (93 mg) was subjected to repeated preparative HPLC (MeOH/H_2O, 2:8 and 15:85) to afford ailanthone (**4**, 32 mg, 0.000 098%). Crystals (18.8 mg) from a MeOH solution of fraction 12-2-4 (143 mg) were purified by preparative HPLC (MeOH/H_2O, 2:8) to afford shinjudilactone (**3**, 16.3 mg, 0.000 049%).

Dissolving subfraction 13 (5.83 g) in MeOH afforded crystals, which were recrystallized from MeOH to afford shinjulactone B (441 mg, 0.0013%). The mother liquor was subjected to column chromatography on Sephadex LH-20 to give four fractions: 13-1 (286 mg), -2 (1.45 g), -3 (2.22 g), and -4 (1.08 g). Preparative HPLC (MeOH/H_2O, 2:8) of fraction 13-2 (1.45 g) gave seven fractions: 13-2-1 (163 mg), -2 (188 mg), -3 (46 mg), -4 (48 mg), -5 (122 mg), -6 (82 mg), and -7 (636 mg). Fraction 13-2-2 (188 mg) then was subjected to preparative TLC ($CHCl_3$/MeOH/H_2O) to give seven fractions: 13-2-2-1 (32 mg), -2 (62 mg), -3 (35 mg), -4 (9 mg), -5 (45 mg), -6 (12 mg), and -7 (8 mg). Fraction 13-2-2-3 (35 mg) was purified by HPLC (MeOH/H_2O, 15:85) to afford the new quassinoid, ailantinol B (**2**, 7.2 mg, 0.000 021%), as colorless needles. Similar treatment of fraction 13-2-2-4 (9 mg) afforded $\Delta^{13(18)}$-dehydroglaucarubolone (7.6 mg, 0.000 023%). Fraction 13-3 (2.22 g) was subjected to preparative HPLC to give eight fractions. Crystals obtained from a MeOH solution of fraction 13-3-6 (318 mg) were recrystallized from MeOH to afford shinjulactone B (210 mg, 0.000 63%); the total amount of shinjulactone B was 651 mg (0.0019%).

Ailantinol A (1): colorless needles; mp 193−195 °C; $[\alpha]^{30}_D$ +77° (*c* 0.03, MeOH); UV (EtOH) λ_{max} 235 (ϵ 10 200) nm; IR (KBr) ν_{max} 3450 (OH), 1800 (γ-lactone C=O), 1750 and 1730 (δ-lactone and ester C=O), and

1670 (α,β-unsaturated C=O) cm^{-1}; EIMS *m/z* $[M]^+$ 406 (85%); HREIMS *m/z* $[M]^+$ 406.1611, calcd for $C_{21}H_{26}O_8$ 406.1597; ^1H- and ^{13}C-NMR data, see Tables 1 and 2.

Ailantinol B (2): colorless needles; mp 149−152 °C; $[\alpha]^{26}_D$ +71° (*c* 0.02, MeOH), UV (MeOH) λ_{max} 240 (ϵ 8700) nm; IR (KBr) ν_{max} 3400 (OH), 1720 (δ-lactone C=O), and 1670 (α,β-unsaturated C=O) cm^{-1}; HREIMS *m/z* $[M]^+$ 394.1628, calcd for $C_{20}H_{26}O_8$ 394.1628; ^1H- and ^{13}C-NMR data see Tables 1 and 2.

All of the known quassinoids isolated in this experiment were identified from their IR, UV, MS, and NMR (^1H, ^{13}C, DEPT, $^1H-^1H$ COSY, and $^{13}C-^1H$ COSY) spectra.

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