Three New Furoquinoline Alkaloids from the Leaves of *Boninia glabra*

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Three novel furoquinoline alkaloid oxogeranyl ethers (1—3) and one known furoquinoline alkaloid (4) were isolated from the leaves of *Boninia glabra*, an endemic plant of the Bonin Islands. Their structures were elucidated on the basis of spectroscopic analysis.

Key words *Boninia glabra*; furoquinoline alkaloid; Bonin Island; leaf; Rutaceae

Boninia glabra Planchon, which belongs to the family Rutaceae, is indigenous to the Bonin Islands in Japan.[1] No phytochemical study of the plant has been made to date. As part of our phytochemical studies on the Bonin Islands,[2] the chemical components of an MeOH extract obtained from the leaves of *B. glabra* were investigated. As a result, three new furoquinoline alkaloid oxogeranyl ethers (**1**—**3**) were isolated, along with a known furoquinoline alkaloid (**4**). This paper describes the isolation and structural elucidation of these components. After column chromatography and HPLC separation of the $CHCl_3$-soluble part of the MeOH extract, compounds (**1**—**3**) were isolated together with a known furoquinoline alkaloid, skimmianine (**4**).[3,4] Identification of the known compound was achieved by comparisons with previously reported physical and spectral data.

Compound **1** exhibited a molecular formula of $C_{22}H_{23}NO_4$ by HR-EI-MS and had IR absorption at 1670 cm^{-1} (conjugated ketone). The ^{1}H-NMR spectrum of **1** (Table 1), analyzed with the aid of 2D-NMR studies [^{1}H–^{1}H shift-correlated spectroscopy (COSY) and nuclear Overhauser enhancement spectroscopy (NOESY) experiments], indicated the presence of five aromatic protons comprised of three protons [δ 7.07 (dd, J=9.3, 2.5 Hz), 7.32 (d, J=2.5 Hz), and 8.12 (d, J=9.3 Hz)] on a benzene ring and two protons [δ 7.02 (d, J=2.8 Hz) and 7.54 (d, J=2.8 Hz)] on a furan ring, together with one methoxy-methyl (δ 4.40) on an aromatic ring. The ^{1}H-NMR spectrum also revealed signals due to three vinyl methyls (δ 1.89, 2.03, 2.07), two olefinic protons (δ 6.08, 6.16), and an oxygenated ethylene [δ 3.17 (t, J=6.5 Hz) and 4.32 (t, J=6.5 Hz)]. In addition to these units, the ^{13}C-NMR spectrum of **1** (Table 1), analyzed with the aid of heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple-bond correlation spectroscopy (HMBC) experiments, exhibited signals due to one carbonyl carbon (δ 190.8) and eight quaternary carbons (δ 101.9, 113.4, 147.7, 154.5, 155.1, 156.9, 160.3, 164.5). On the aromatic ring, the ^{1}H- and ^{13}C-NMR spectral data of **1** were in close agreement with those of evolitrine (**5**)[5,6] and other 7-*O*-substituted-4-methoxyfuroquinolines,[7,8] suggesting that **1** is a 7-*O*-substituted-4-methoxyfuroquinoline alkaloid containing a C_{10} side-chain. Precise analysis of ^{1}H- and ^{13}C-NMR revealed the presence of the 5-oxogeranyl [–O–$CH_2CH_2C(CH_3)$=

Table 1. ^{1}H- (600 MHz) and ^{13}C- (150 MHz) NMR Spectral Data of **1**—**3** in $CDCl_3$

No.	**1**		**2**		**3**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	7.54 (1H, d, 2.8)	142.4	7.57 (1H, d, 2.7)	142.5	7.57 (1H, d, 2.8)	142.5
3	7.02 (1H, d, 2.8)	104.8	7.04 (1H, d, 2.7)	104.9	7.05 (1H, d, 2.8)	104.8
3a		101.9		102.0		102.0
4		156.9		157.0		157.0
4a		113.4		113.5		113.5
5	8.12 (1H, d, 9.3)	123.5	8.14 (1H, d, 9.3)	123.7	8.15 (1H, d, 9.3)	123.6
6	7.07 (1H, dd, 9.3, 2.5)	116.8	7.07 (1H, dd, 9.3, 2.6)	116.9	7.10 (1H, dd, 9.3, 2.5)	117.0
7		160.3		160.0		160.1
8	7.32 (1H, d, 2.5)	107.0	7.32 (1H, d, 2.6)	106.7	7.33 (1H, d, 2.5)	107.0
8a		147.7		147.6		147.7
9a		164.5		164.5		164.5
1′	4.32 (2H, t, 6.5)	67.2	4.27 (2H, t, 6.6)	65.7	4.71 (2H, d, 6.3)	64.8
2′	3.17 (2H, t, 6.5)	33.4	2.68 (2H, t, 6.6)	40.2	5.68 (1H, tq, 6.3, 1.0)	123.9
3′		154.5		152.9		135.7
4′	6.16 (1H, s)	127.7	6.16 (1H, s)	127.3	3.17 (2H, s)	55.1
5′		190.8		191.5		198.2
6′	6.08 (1H, m)	126.0	6.08 (1H, m)	126.2	6.13 (1H, m)	122.8
7′		155.1		154.9		156.7
8′	1.89 (3H, d, 1.0)	27.8	1.89 (3H, d, 1.3)	27.8	1.86 (3H, d, 1.2)	27.7
9′	2.17 (3H, d, 1.0)	20.7	2.17 (3H, d, 1.0)	20.7	2.15 (3H, d, 1.0)	20.8
10′	2.03 (3H, d, 1.0)	26.7	2.26 (3H, d, 1.3)	19.3	1.80 (3H, d, 1.0)	17.1
OCH_3	4.40 (3H, s)	58.9	4.43 (3H, s)	58.9	4.43 (3H, s)	59.0

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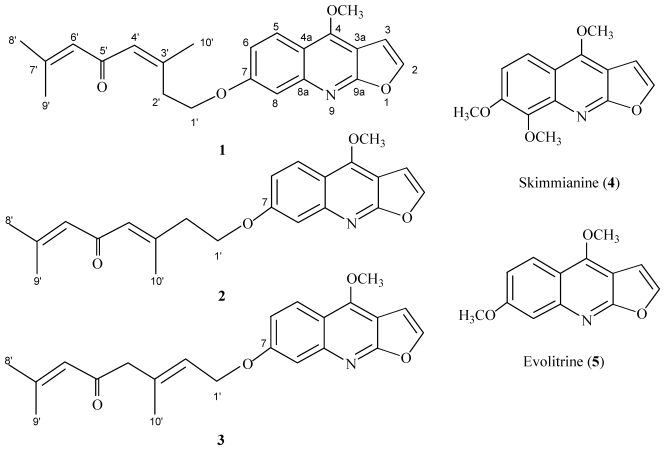

Fig. 1

CHCOCH=C(CH$_3$)$_2$] side-chain[9,10] in **1**. The observation of significant fragment ions at *m/z* 151 due to 5-oxogeranyl ($C_{10}H_{15}O$) group and *m/z* 215, resulting from the loss of a $C_{10}H_{15}O$ unit with a hydrogen transfer[11] in the EI-MS, also supported the structure of the side-chain. Stereochemistry of the double bond in **1** was established as follows. In the NOE-difference experiments, **1** showed prominent NOE correlations between 10′-H$_3$ and 4′-H, indicating the *Z*-stereochemistry of the 3′, 4′ double bond[9,10] in **1**. This assignment was also supported by the ^{13}C-NMR chemical shift value of the C-10′ (δ 26.7). Since the 10′-methyl carbon signal of such 5*Z*-isomer is shifted upfield (δ_C>20 ppm) compared with that of the corresponding 5*E*-isomer (δ_C<20 ppm).[9,10,12] The unambiguous structure of the side-chain in **1** was established from HMBC experiments to indicate significant correlation peaks between 1′-H$_2$/C-2′, C-3′, C-7, between 2′-H$_2$/C-1′, C-3′, C-4′, C-10′, between 4′-H/C-2′, C-5′, C-10′, and between 6′-H/C-5′, C-8′, C-9′. The connection of the 5-oxogeranyl side-chain to C-7 on the furoquinoline ring was revealed by the HMBC correlation peak between 1′-H$_2$/C-7 as well as NOE correlation peaks between 1′-H$_2$/6-H and 1′-H$_2$/8-H. On the basis of these results, the structure of compound **1** is shown in Fig. 1.

Compound **2** had the same molecular formula ($C_{22}H_{23}NO_4$) as **1** based on HR-EI-MS. The NMR spectrum of **2** (Table 1) showed the presence of the same functional groups and same moieties as those of **1**. However, the chemical shifts due to 2′-H$_2$ and 10′-H$_3$ in **2** [δ 2.68 (t, *J*=6.6 Hz) and 2.26 (d, *J*=1.3 Hz), respectively] were remarkably different from those of **1** [δ 3.17 (t, *J*=6.5 Hz) and 2.03 (d, *J*=1.0 Hz), respectively] (Table 1), suggesting a change in the *E*/*Z* geometry of the 3′, 4′ double bond. The stereochemistry of the 3′, 4′ double bond in **2** was determined by the NOE-difference experiments. As a result, **2** exhibited the prominent cross peaks between 2′-H$_2$/4′-H to establish *E*-configuration of the 3′, 4′ double bond.[9,10,12] This stereochemistry was also supported by the carbon chemical shift of C-10′ (δ 19.3) in **2**.[9,10,12] Finally, HMBC experiments of **2** indicated essentially the same correlation peaks as those observed in **1**. Based on the evidence, the structure of compound **2** is proposed as shown in Fig. 1.

Compound **3** had the same molecular formula ($C_{22}H_{23}NO_4$) as **1** and **2** based on HR-EI-MS. The ^{1}H-NMR spectrum of **3** (Table 1) exhibited similar signals to **1** and **2**. However, the presence of a singlet methylene (δ 3.17) and an oxygenated methylene [δ 4.71 (d, *J*=6.3 Hz)] suggested that **3** is a regioisomer of **1** and **2** as a result of double-bond migration. Precise analysis of ^{1}H- and ^{13}C-NMR revealed the presence of a 2′, 3′ double bond in **3** instead of the 3′, 4′ double bond in **1** and **2**. The stereochemistry of the double bond was confirmed by the NOE-difference experiments to show correlation peaks between 2′-H/4′-H$_2$.[9,10,12] These results, as well as the carbon chemical shift of C-10′ (δ 17.1),[9,10,12] indicated the *E*-configuration of the 2′, 3′ double bond in **3**. Based on the evidence, the structure of compound **3** is shown in Fig. 1.

Experimental

All melting points were recorded on a Yanagimoto micro melting point apparatus without correction. ^{1}H- and ^{13}C-NMR spectra were measured on a JEOL JNM-ECA 600 spectrometer (^{1}H at 600 MHz and ^{13}C at 150 MHz). Chemical shifts are given in δ values (ppm) relative to tetramethylsilane (TMS) as an internal standard. EI- and HR-EI-MS spectra (at 30 eV) were obtained using a JEOL JMS-700T spectrometer. IR spectra were measured with a JASCO FT/IR-410 spectrometer with KBr disks. For column chromatography, silica gel 60 (230—400 mesh, Merck) was used. Preparative HPLC was performed on a JAI LC-908 instrument with a RI-50 differential refractometer and a JAIGEL-ODS column.

Plant Material The leaves of *Boninia glabra* Planchon were collected in March 2002 in Chchizima in the Bonin Islands, Japan and a voucher specimen (No. 194) was deposited in the Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Setsunan University.

Extraction and Isolation Crushed leaves (139 g) were extracted with MeOH (3×1.5 l) at room temperature. The MeOH solution was evaporated off to give an extract (41.9 g). The MeOH extract (41.0 g) was suspended with H$_2$O (700 ml) and the aqueous suspension was extracted with CHCl$_3$ (3×0.5 l). The resulting CHCl$_3$ extract (11.1 g) was chromatographed on silica gel (300 g) with hexane–EtOAc with increasing EtOAc concentration and EtOAc to give 10 fractions (Frs. A—J). Fr. G (0.15 g), eluted with hexane–EtOAc (1 : 1), was purified by reversed phase preparative HPLC [MeOH–H$_2$O (10 : 1)] to afford **1** (19.4 mg). Fr. H (0.40 g), eluted with hexane–EtOAc (1 : 1), was purified by reversed phase HPLC [MeOH–H$_2$O (10 : 1)] to isolate **1** (58.4 mg), **2** (32.3 mg), and **3** (6.8 mg), respectively. Fr. J (0.26 g), eluted with EtOAc, was further separated by reversed HPLC eluted with MeOH–H$_2$O (5 : 1) to afford **4** (39.0 mg).

Compound 1 (**1**): Yellow amorphous solid; IR (KBr) cm^{-1}: 2930, 1670, 1620, 1600; EI- and HR-EI-MS *m/z* (rel. int.): 365.1627 [M$^-$, Calcd for $C_{22}H_{23}NO_4$, 365.1627 (26)], 282 (20), 215 (38), 200 (8), 151 (100), 83 (10); ^{1}H- and ^{13}C-NMR data see Table 1.

Compound 2 (**2**): Pale yellow crystals, mp 150—153 °C; IR (KBr) cm^{-1}: 2940, 1670, 1620, 1600; EI- and HR-EI-MS *m/z* (rel. int.): 365.1626 [M$^+$, Calcd for $C_{22}H_{23}NO_4$, 365.1627 (26)], 282 (49), 215 (81), 200 (16), 151 (100), 83 (18); ^{1}H- and ^{13}C-NMR data see Table 1.

Compound 3 (**3**): Yellow amorphous solid; EI- and HR-EI-MS *m/z* (rel. int.): 365.1626 [M$^+$, Calcd for $C_{22}H_{23}NO_4$, 365.1627 (8)], 282 (13), 215 (100), 200 (21), 151 (38), 83 (13); ^{1}H- and ^{13}C-NMR data see Table 1.

Skimmianine (**4**): Yellow crystals, mp 177—179 °C; EI- and HR-EI-MS *m/z* (rel. int.): 259.0840 [M$^+$, Calcd for $C_{14}H_{13}O_4N$, 259.0844 (85)], 244 (100), 230 (44); ^{1}H-NMR (in CDCl$_3$): 7.57 (1H, d, *J*=2.8 Hz, 2-H), 7.03 (1H, d, *J*=2.8 Hz, 3-H), 8.01 (1H, d, *J*=9.4 Hz, 5-H), 7.23 (1H, d, *J*=9.4 Hz, 6-H), 4.43 (3H, s, 4-OCH$_3$), 4.03 (3H, s, 7-OCH$_3$), 4.12 (3H, s, 8-OCH$_3$). The ^{13}C-NMR data of **4** were consistent with those reported for skimmianine.[3,4]

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