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Neovibsanines A and B, Unprecedented Diterpenes from *Viburnum awabuki*

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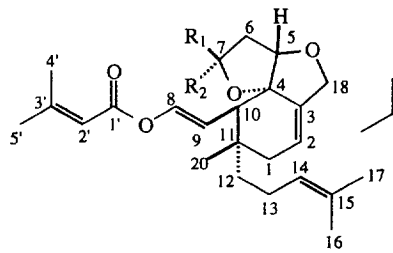
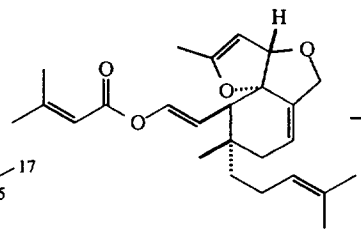
Abstract: Neovibsanines A and B, isolated from the leaves of *Viburnum awabuki*, are unprecedented tricyclic diterpenoids, which are presumably biosynthesized via consecutive ring cleavage and cyclization from vibsanine B. Their relative structures have been established by extensive analysis of spectroscopic data and photochemical reaction of vibsanine B. Copyright © 1996 Elsevier Science Ltd

In 1980, Kawazu[1] reported the isolation of a piscicidal compound, vibsanine A, and a plant growth inhibitor, vibsanine B (**3**) from the leaves of *Viburnum awabuki*, poison plants used for catching fish in Okinawa. Since vibsanines A and B are the first examples of diterpenes with an 11-membered carbon ring like humulene-type sesquiterpenes, we have proposed the new term of "vibsanine" for this type of diterpenes.[2] In our continuing search for antioxidative substances in natural products,[3] the methanol extract of the leaves of *V. awabuki* has been found to show antioxidative property, and thus we have reinvestigated the chemical constituents of *V. awabuki*, resulting in the isolation of unprecedented diterpenes **1** and **2** named neovibsanines A and B. In this paper, we describe the structural elucidation of **1** and **2**, and photochemical conversion to demethoxydehydroneovibsanine (**1a**) from vibsanine B (**3**).

Neovibsanine A (**1**),[4] obtained as colorless needles, has the molecular formula $C_{26}H_{38}O_5$ established by HR-FAB-MS and ^{13}C NMR data (Table 1), indicating 8 degrees of unsaturation. The ^1H and ^{13}C NMR data (Table 1) of **1** showed the presence of six tertiary methyl groups [δ_H 0.91, 1.34, 1.44, 1.60, 1.66, and 2.03 (each s)], a methoxy group (δ_H 3.32; δ_C 50.2), an oxymethylene [δ_H 4.14 (dd, J = 10.8, 1.1 Hz) and 4.53 (ddt, J = 10.8, 3.0, 2.1 Hz); δ_C 70.3] and an oxymethine [δ_H 4.56 (dd, J = 4.4 Hz); δ_C 87.7] . In addition to the above



1 $R_1 = OCH_3$, $R_2 = CH_3$
2 $R_1 = CH_3$, $R_2 = OCH_3$



1a

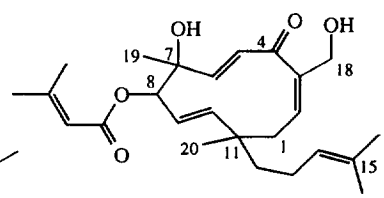


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Table 1. ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR data for **1**, **2**, and **1a**

	1		**2**		**1a**
Carbon	δ_H	δ_C	δ_H	δ_C	δ_C
1	1.90 (2H, dd, 3.0, 2.1 Hz)	34.7	1.73 (2H, dd, 3.7, 2.1 Hz)	37.6	37.5
2	5.22 (ddd, 3.0, 3.0, 1.1 Hz)	120.6	5.31 (ddd, 3.7, 2.1, 0.7)	120.9	120.9
3		137.8		137.9	136.4
4		90.7		91.6	91.8
5	4.56 (d, 4.4 Hz)	87.7	4.62 (d, 5.6 Hz)	86.4	89.0
6	2.29 (dd, 11.8, 4.4 Hz)	45.4	1.66 (dd, 13.9, 5.6 Hz)	46.6	96.6
	2.70 (d, 11.8 Hz)		2.42 (d, 13.9 Hz)		
7		110.9		108.9	159.4
8	7.50 (d, 12.4 Hz)	137.4	7.50 (d, 12.5 Hz)	137.8	138.5
9	5.00 (dd, 12.4, 11.7 Hz)	113.1	5.22 (dd, 12.5, 11.7 Hz)	113.0	112.3
10	2.24 (d, 12.0 Hz)	47.7	2.35 (d, 11.7 Hz)	47.1	45.0
11		35.5		35.8	35.5
12	1.61 (m)	39.7	1.18 (ddd, 13.8, 10.0, 5.0 Hz)	41.5	41.2
	1.85 (m)		2.19 (ddd, 13.8, 10.0, 3.8 Hz)		
13	2.02 (m)	23.6	2.03 (m)	23.1	23.3
	2.21 (m)		2.09 (m)		
14	5.29 (t, 6.0 Hz)	126.3	5.28 (t, 6.0 Hz)	126.2	126.1
15		130.7		130.3	130.2
16	1.60 (s)	17.9	1.64 (s)	17.9	17.9
17	1.66 (s)	26.0	1.71 (s)	25.9	25.9
18	4.14 (dd, 10.8, 1.1 Hz)	70.3	4.16 (dd, 10.3, 0.7 Hz)	70.5	67.6
	4.53 (ddt, 10.8, 3.0, 2.1 Hz)		4.80 (ddt, 10.3, 2.1, 2.1 Hz)		
19	1.44 (s)	24.0	1.32 (s)	23.0	13.7
20	0.91 (s)	26.3	0.90 (s)	25.9	26.8
1'		163.3		163.3	163.1
2'	5.65 (qq, 1.4, 1.4 Hz)	115.4	5.66 (qq, 1.2, 1.2 Hz)	115.2	115.3
3'		159.5		159.7	159.6
4'	2.03 (d, 1.4 Hz)	20.4	2.05 (d, 1.2 Hz)	20.3	20.2
5'	1.34 (d, 1.4 Hz)	27.1	1.38 (d, 1.2 Hz)	27.0	27.2
MeO	3.32 (s)	50.	3.15 (s)	48.8	

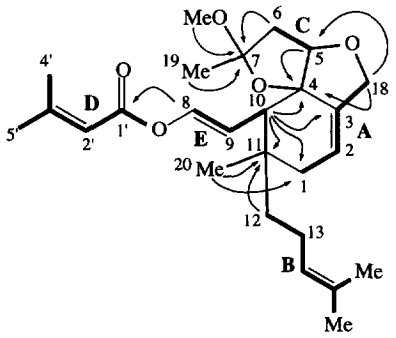

Fig. 1. Connectivities established by 2D NMR (600 MHz) of **1**. Bold line: DQF-COSY, TOCSY and HMQC; Arrows denote the HMBC correlations between the proton (tail) and carbons (head).

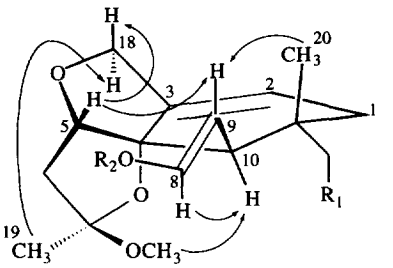

Fig. 2. Realtive stereochemistry of neovibsanine A (**1**) based on 2D NOESY and difference NOE.

fragments, the ^{13}C and HMQC spectra indicated distinct resonances due to a conjugated ester carbonyl at δ_C 163.3, three trisubstituted olefins (δ_H 5.22, δ_C 120.6 and 137.8; δ_H 5.29, δ_C 126.3 and 130.7; δ_H 5.65, δ_C 115.4 and 159.5), one disubsituted olefin [δ_H 7.50 (d, J = 12.4 Hz) and 5.00 (dd, J = 12.4, 11.7 Hz); δ_C 137.4 and 113.1], four methylenes (δ_C 23.6, 34.7, 39.7, 45.4), and three sp^3 quaternary carbons including two oxygenated carbons (δ_C 35.5, 90.7 and 110.9), the latest one of which should be assigned as a ketal function due to its low-field resonance. Detailed analysis of DQF-COSY, HMQC and TOCSY gave five partial structures **A** ~ **E** (Fig. 1, in boldface). The double bond in the **A** unit should take *Z*-geometry due to the observation of NOE between H-18 and H-2, whereas the *E* double bond in the **E** part was evident from a H-8/H-9 vicinal coupling constant (J = 12.4 Hz) as well as significant NOE between H-8 and H-10. The presence of the partial structure **D** which corresponded to a β,β-dimethylacryl group was additionally supported by the observation of the prominent fragment ion peak at *m/z* 83 in the MS. Eventually, the carbons which are not involved in the structural fragments turn out to be three sp^3 quaternary carbons. Accordingly, the HMBC experiment was employed to assemble the partial units through the quaternary carbons. The resultant long-range ^{13}C–^1H correlations are shown in Fig. 1. The HMBC correlation of the C-1' ester carbonyl with H-8 indicated that the β,β-dimethylacryl moiety **D** linked to C-8 of the unit **E** via an enol ester bond. The C-5 and H-5 resonances correlated to the H-18 signal in the unit **A** and the C-4 quaternary carbon one at δ_C 90.7, respectively, which in turn showed clear cross peak to each other, thereby indicating the presence of a hydrofuran ring on the C-3 and C-4 positions through an ether bond between C-5 of the unit **C** and C-18 of the unit **A**. Additionally, the C-7 ketal carbon showed cross peaks to OMe, 19-Me and H-6, and thus the C-7 ketal carbon, which connected to OMe, 19-Me, and C-6 of the unit **C**, could appoint the counterpart of the remaining ether bond to the C-4 quaternary carbon involving in the hydrofuran ring. Thereby, these HMBC correlations led to the construction of another hydrofuran ring on the C-5 and C-6 positions via an ether linkage between C-4 and C-7. Hence, two hydrofuran rings were clarified to be fused in the opposite direction on the C-4 and C-5 positions. Moreover, treatment of **1** with Ac_2O and pyridine afford the dihydrofuran **1a**[5] by the elimination of the methanol, supporting the incorporation of ketal carbon into the hydrofuran ring. Taking account of a tricyclic structure for **1**, the HMBC correlations around the remaining C-11 quaternary carbon, as shown in Fig. 1, disclosed that a 6-membered ring including the partial units **A**, **B** and **E** was constructed by connecting C-11 to 20-Me, C-1 (**A**), C-10 (**E**) and C-12 (**B**), respectively. Thus, the connection of the entire carbons was achieved as an unprecedented tricyclic diterpene skeleton, as shown in Fig. 1.

The relative stereochemistry of **1** was elucidated on the basis of NOE correlations from NOESY and difference NOE experiments, as shown in Fig. 2. Thus, the spectral and chemical data aforementioned corroborated the structure **1** for neovibsanine A.

Neovibsanine B (**2**)[6] has the same molecular formula as that of **1**, and the IR and UV of **2** displayed the presence of the same functional groups as those of **1**. The ^1H and ^{13}C NMR data (Table 1) were also very similar to those of **1**. Moreover, 2D NMR experiments elaborated the spin systems associated with all the partial units presented in **1**. Detailed analysis of the HMBC for **2** made up the same plane structure as **1**. The above spectral similarity suggested that **2** is an epimer on the C-7 position in **1**. In contrast to **1**, the OMe resonance at δ_H 3.15 showed distinct cross peak to H-18α at δ_H 4.80, whereas an NOE correlation was observed between 19-Me (δ_H 1.32) and H-10 (δ_H 2.35). These results supported the epimeric nature of **2** on the C-7 position of **1**. Hence, neovibsanine B (**2**) was assigned as the α-methoxyl congener of **1**.

To our knowledge, diterpenoids which are composed of the carbon skeleton like neovibsanines A and B have not been reported so far and these compounds are unable to categorize to the known diterpenoids.[7]

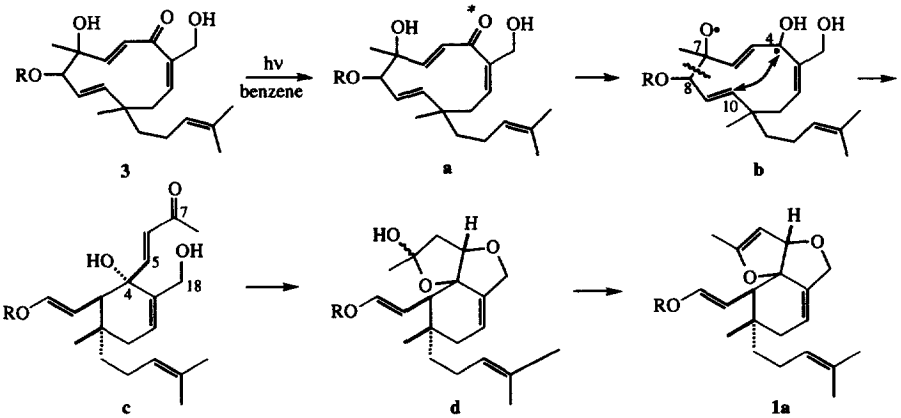

Fig. 3. Photochemical conversion of vibsanine B to neovibsanine skeleton

Although it is postulated that the 11-membered vibsanine B (**3**) which co-occurs in the title plant may be a biosynthetic precursor for **1** and **2**, we have no evidence to propose plausible pathway of their biosytnhesis. It is, however, worthy of note that the skeleton of neovibsanine can be photochemically derived from vibsanine B (**3**). Namely, irradiation of **3** in benzene solution by high pressure Hg lamp afforded **1a**, which was identical in all respects with **1a** obtained from neovibsanine A (**1**). Excited carbonyl presumably initiates a consecutive bond cleavage and reforms by the hydrogen abstraction of the C-7 hydroxyl group, as shown in Fig. 3, to give rise to **1a**. This result throws light on the biosynthesis of neovibsanines.

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4. Neovibsanine A (**1**): mp 56–57°C; $[\alpha]_D^{23}$ –34.8° (*c* 0.6, $CHCl_3$); $\nu_{max}cm^{-1}$: 1734 (ester C=O), 1647 (C=C); λ_{max}^{EtOH}nm: 224 (ε 14500); FAB-MS: *m/z* 453 $[M+Na]^+$, 341 (100), 83 (100): HR-FAB-MS: *m/z* 453.2617 $[M+Na]^+$, calcd. 453.2617 for $C_{26}H_{38}O_5Na$.
5. **1a**: $[\alpha]_D^{23}$ 78.8 (*c* 0.16, $CHCl_3$); $\nu_{max}cm^{-1}$: 1728 (ester C=O), 1644 (C=C); λ_{max}^{EtOH}nm: 216 (ε 25000); EI-MS: *m/z* 398 $[M]^+$, 83 (100): HR-EI-MS: *m/z* 398.2437 $[M]^+$, calcd. 398.2417 for $C_{25}H_{34}O_4$. ^1H NMR (600 MHz, C_6D_6): δ 0.90 (3H, s, H_3-20), 1.12 (1H, ddd, *J* = 13.4, 12.2, 4.9 Hz, H-12), 1.36 (3H, d, *J* = 1.2 Hz, H_3-5'), 1.61 (3H, s, H_3-19), 1.62 (3H, s, H_3-16), 1.71 (3H, s, H_3-17), 1.72 (2H, d, *J* = 2.7 Hz, H-1), 2.01 (1H, m, H-13), 2.03 (3H, d, *J* = 1.2 Hz, H_3-4'), 2.10 (1H, m, H-13), 2.25 (1H, ddd, *J* = 13.4, 10.0, 5.0 Hz, H-12), 2.47 (1H, d, *J* = 11.2 Hz, H-10), 4.08 (1H, d, *J* = 10.3 Hz, H-18), 4.25 (1H, dd, *J* = 10.3, 2.0 Hz, H-18), 4.63 (1H, d, *J* = 1.2 Hz, H-6), 5.27 (1H, dd, *J* = 12.5, 11.2 Hz, H-9), 5.28 (1H, m, H-1 4), 5.32 (1H, dt, *J* = 2.7, 2.0 Hz, H-2), 5.30 (1H, d, *J* = 1.2 Hz, H-5), 5.62 (1H, qq, *J* = 1.2, 1.2 Hz, H-2'), 7.47 (1H, d, *J* = 12.5 Hz, H-8).
6. Neovibsanine B (**2**): $[\alpha]_D^{23}$ 44.4° (*c* 0.2, $CHCl_3$); $\nu_{max}cm^{-1}$: 1732 (ester C=O), 1647 (C=C); λ_{max}^{EtOH}nm: 225 (ε 17600); FAB-MS: *m/z* 453 $[M+Na]^+$, 83 (100): HR-FAB-MS: *m/z* 453.2611$[M+Na]^+$, calcd. 453.2617 for $C_{26}H_{38}O_5Na$.
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