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Neovibsanin C, a macrocyclic peroxide-containing neovibsane-type diterpene from *Viburnum awabuki*

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Abstract

A unique neovibsane-type diterpene, neovibsanin C (**1**), isolated from the leaves of *Viburnum awabuki*, has been demonstrated to have an unprecedented structure macrocyclized via an *endo*-peroxide by extensive analyses of spectral data and chemical degradation as well as synthesis of **1** from neovibsanin B (**3**).

Keywords: vibsane-type diterpene; neovibsanin; *endo*-peroxide; *Viburnum awabuki*.

Vibsane-type diterpenes, which consist of a fumulane-type carbon skeleton with an additional isoprene unit, are quite rare in nature and their occurrence has been limited to *Viburnum awabuki*[1] (Caprifoliaceae) and the liverwort *Odontoschisma denudatum*.[2] The carbon skeletons of vibsane-type diterpenes can be further divided into three subgroups characterized by an 11-membered ring, a seven-membered ring, and a rearranged type and are represented by vibsanin B (**4**), vibsanin C,[3] and neovibsanins A (**2**) and B (**3**),[4] respectively. Hence, this structural diversity of vibsane-type diterpenes has captivated us so much that we keep on studying the chemical components of *Viburnum* species.[5] Our ongoing chemical studies[6] on the methanol extract of the leaves of *V. awabuki* have resulted in the isolation of an unprecedented macrocyclic neovibsane-type diterpene **1** named neovibsanin C. In this communication, we report the macrocyclic peroxy structure of **1** established by spectroscopic data and chemical degradation as well as by synthesis from neovibsanin B (**3**).

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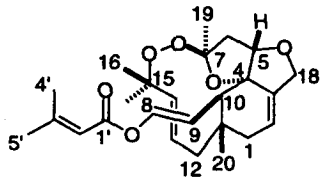

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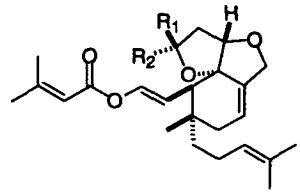
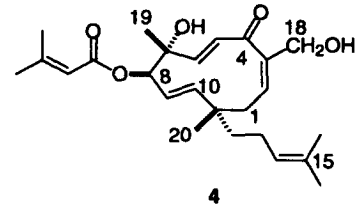


2 R_1 = OMe, R_2 = Me
3 R_1 = Me, R_2 = OMe



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Neovibsanin C (**1**),[7] has the molecular formula $C_{25}H_{34}O_6$ established by HR-FABMS, consistent with nine unsaturation units. The spectral data of **1** (Table 1) showed the presence of four tertiary methyl groups (δ 0.93, 1.16, 1.47, and 1.81), a β,β-dimethylacrylate group (δ 1.37, 2.04, 5.66; δ 163.1, 159.8, 115.0; *m/z* 83; 1730 cm^{-1}), two kinds of disubstituted olefins [for Δ^8 δ 5.02 (dd, *J*=12.6, 11.8), 7.43 (d, *J*=12.6); δ 113.2, 136.9: for Δ^{13} δ 5.46 (ddd, *J*=15.7, 11.5, 4.1), 5.88 (dd, *J*=15.7, 1.6); δ 125.4, 143.1], a trisubstituted olefin (δ 5.14; δ 119.4, 137.4), an oxymethylene [δ 4.12 (brdd, *J*=11.8, 1.0), 4.54 (ddt, *J*=11.8, 2.2, 2.0)], an oxymethine [δ 4.26 (d, *J*=3.8)] in addition to four quaternary carbons (δ 115.6, 90.9, 81.6, 35.5). These spectral data were very similar to those of neovibsanins A (**2**) and B (**3**) except for a C-12~C-17 isoprene moiety and extremely low chemical shift values of a ketal-type C-7 (δ 115.6) and oxygen-bearing C-15 (δ 81.6) carbons. In fact, routine analyses of ^1H–^1H COSY, HMQC and HMBC as shown in Fig. 1 elaborated all the structure fragments closely related to **2** and **3** except for a different C6 unit containing a (*E*)-double bond ($J_{13,14}$=15.7 Hz) at C-12~C-17. Although all the spectral data including the HMBC failed to connect two oxygen atoms on the C-7 and C-15 positions to appropriate positions, only structure **1** macrocyclized through a peroxy group between the C-7 and C-15 positions was accepted and thus was able to satisfy nine degrees of unsaturation, the absence of hydroxy group (IR) and the low chemical shifts of C-7 and C-15 for neovibsanin C. In order to substantiate the presence of the *endo*-peroxy group between C-7 and C-15, reduction of **1** with Zn in EtOH–AcOH was attempted to give rise to **6**,[8] C-7 and C-15 of which were found to be high-field shifted to δ 108.6 and 70.3, respectively. This result supported the presence of the *endo*-peroxy which constructed the cross-linkage between C-7 and C-15. Further, **6** was treated with anhydrous MeOH in the presence of *p*TsOH to yield **7**, which was also readily derived from neovibsanin B (**3**) as follows: compound **3** was subjected to photooxidative conditions (singlet oxygen) giving rise to **5**, the hydroperoxy group of which was reduced with Ph_3P to yield **7** quantitatively. The both compounds were identical in all the respects. Finally, the relative stereochemistry of **1** was clarified by a nuclear Overhauser exchange spectroscopy (NOESY), as shown in Fig. 2. Thus the spectral data and the chemical conversion aforementioned determined the structure **1** for neovibsanin C.

Neovibsanin C (**1**) consists of an 11-membered cyclic structure closed via an *endo*-peroxide between C-7 and C-15 in **5**. A MM2 calculation of **5** indicates that the most stable conformation disposes the C-12~C-17 side chain over the left-hand tetrahydrofuran ring, resulting in the hydroperoxy group on C-15 being in close proximity to the C-7 ketal carbon. Having this result in mind, we have attempted to synthesize **1** directly from **5** under acidic conditions (Scheme 1). After several efforts failed, we found that when **5** was treated with *p*TsOH in anhydrous benzene at room temperature for 5 min, it gave **1**[9] in 68% yield. Thus this synthesis of **1** from **3** has established that **1** has the same absolute configuration as **2** and **3**.

Although a number of natural products having an *endo*-peroxy group in the molecules have been known,[10] the largest *endo*-peroxy ring is a seven-membered one, representative of which is antimalarial artemisinin.[11] We emphasize that neovibsanin C (**1**) is the first example of a natural product having a macrocyclic peroxy ketal ring. Most natural products having *endo*- or *exo*-peroxy groups exhibit a

Table 1
^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) of neovibsanin C (**1**) in C_6D_6

C	^{1}H	^{13}C	C	^{1}H	^{13}C
1	1.60 (*m*)	37.0	11		35.5
	1.69 (*m*)				
2	5.14 (*m*)	119.4	12	1.98 (*ddd*, 13.2, 4.1, 1.6)	43.7
				2.80 (*dd*, 13.2, 11.5)	
3		137.4	13	5.46 (*ddd*, 15.7, 11.5, 4.1)	125.4
4		90.9	14	5.88 (*dd*, 15.7, 1.6)	143.1
5	4.26 (*d*, 3.8)	86.7	15		81.6
6β	1.99 (*dd*, 14.8, 3.8)	42.1	16	1.16 (*s*)	25.1
6α	2.20 (*d*, 14.8)				
7		115.6	17	1.47 (*s*)	21.8
8	7.43 (*d*, 12.6)	136.9	18β	4.12 (*brdd*, 11.8, 1.6)	70.4
			18α	4.54 (*ddt*, 11.8, 2.2, 2.0)	
9	5.02 (*dd*, 12.6, 11.8)	113.2	19	1.81 (*s*)	25.4
10	2.78 (*d*, 11.8)	42.8	20	0.93 (*s*)	28.0
1'		163.1	4'	2.04 (*d*, 1.1)	20.3
2'	5.66 (*qq*, 1.4, 1.1)	115.0	5'	1.37 (*d*, 1.4)	27.0
3'		159.8			

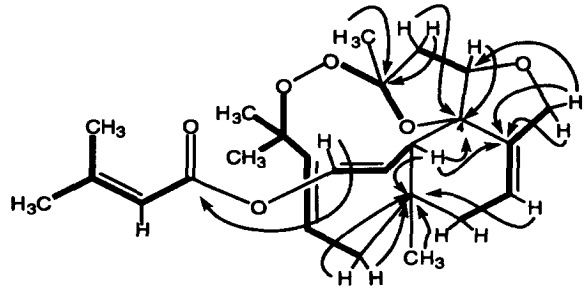


Figure 1. Partial structures (bold line) and HMBC correlations (arrows) of **1**

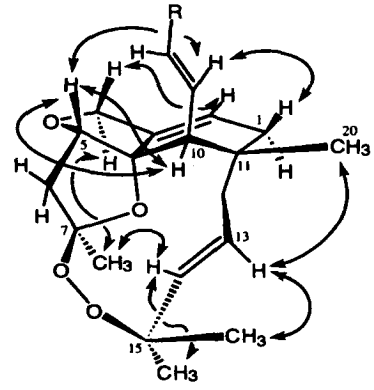
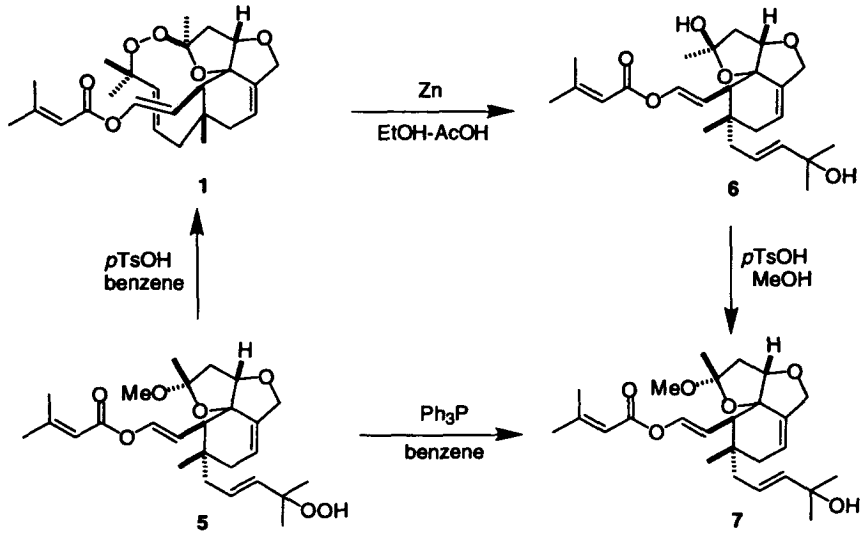


Figure 2. Relative stereochemistry of **1** based on NOESY denoted by arrows



Scheme 1. Chemical correlation of hydroperoxyneovibsanin B (**5**) to neovibsanin C (**1**)

variety of biological activities such as cytotoxicity and antimalaria,[12] so we will characterize a profile of biological activities that **1** may have.[13]

Acknowledgements

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7. Neovibsanin C (**1**) (15 mg) was isolated from the MeOH extract (50 g): $[\alpha]_D^{20}$ +40.5 (0.15, $CHCl_3$); HR-FABMS *m/z* 453.2253 (calcd for $C_{25}H_{34}O_6Na$; found 453.2256); FABMS *m/z* 453 $[M+Na]^+$, 431 $[M+H]^+$, 83; IR (FT) cm^{-1}: 1732 (C=O), 1645 (C=C); UV(EtOH) λ_{max} nm: 244 (ε 4400).
8. Compound **6**: HR-FABMS *m/z* 455.2410 (calcd for $C_{25}H_{36}O_6Na$; found 455.2438); IR (FT) cm^{-1}: 3499 (OH), 1730 (C=O), 1645 (C=C). ^1H NMR (600 MHz, C_6D_6): δ 0.96 (3H, s, H_3-20), 1.35 (3H, d, *J*=1.4 Hz, H_3-5′), 1.37 (3H, s, H_3-19), 1.45 (3H, s, H_3-17), 1.76 (3H, s, H_3-16), 2.01 (3H, d, *J*=1.4 Hz, H_3-4′), 1.59 (1H, brdd, *J*=14.3, 9.9 Hz, H-12), 1.60 (1H, brd, *J*=18.5 Hz, H-1), 1.84 (1H, brd, *J*=18.5 Hz, H-1), 2.32 (1H, brdd, *J*=14.3, 3.8 Hz, H-6), 2.67 (1H, d, *J*=14.3 Hz, H-6), 3.08 (1H, d, *J*=11.8 Hz, H-10), 3.29 (1H, brdd, *J*=14.3, 5.2 Hz, H-12), 4.19 (1H, brd, *J*=12.4 Hz, H-18), 4.51 (1H, d, *J*=3.8 Hz, H-5), 4.58 (1H, brdd, *J*=12.4, 2.2 Hz, H-18), 5.16 (1H, dd, *J*=12.4, 11.8 Hz, H-9), 5.23 (1H, m, H-2),

5.52 (1H, d, J=15.9 Hz, H-14), 5.67 (1H, qq, J=1.4, 1.4 Hz, H-2′), 6.35 (1H, ddd, J=15.9, 9.9, 5.2 Hz, H-13), 7.73 (1H, d, J=12.4 Hz, H-8). ^{13}C NMR (150 MHz, C_6D_6): 20.3 (C-4′), 27.0 (C-20), 27.1 (C-19), 29.5 (C-5′), 30.6 (C-17), 30.8 (C-16), 35.7 (C-11), 37.3 (C-1), 42.6 (C-12), 44.3 (C-6), 45.2 (C-10), 70.3 (C-15), 72.3 (C-18), 87.8 (C-5), 90.0 (C-4), 108.6 (C-7), 112.7 (C-9), 115.2 (C-2′), 120.2 (C-2), 123.9 (C-13), 137.1 (C-3), 137.4 (C-8), 140.9 (C-14), 159.6 (C-3′), 163.1 (C-1′).

9. Synthetic **1**: $[\alpha]_D^{20}$ +40.5 (0.15, $CHCl_3$); all spectral data (IR, ^{1}H and ^{13}C NMR) are identical with those of natural **1**.
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13. No cytotoxicity against KB cells was observed at 100 μM.