Aldovibsanins, Enol Ester Free Vibsane-Type Diterpenes from *Viburnum Odoratissimum*

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Aldovibsanin A (1), 7-epi-aldovibsanin A (2) and aldovibsanin B (3), novel vibsane-type diterpenes without a β,β-dimethylacrylate group, have been isolated from the leaves of *Viburnum odoratissimum*, and their structures have been elucidated by spectroscopic analyses and chemical correlation with vibsanin C (4).

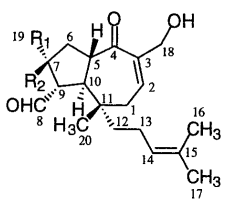
Key words *Viburnum odoratissimum*; Caprifoliaceae; aldovibsanin A; 7-epi-aldovibsanin A; aldovibsanin B; vibsane-type diterpene

Our continuing studies on the chemical constituents of the leaves of *Viburnum awabuki* have resulted in the isolation of a number of vibsane-type diterpenes.[1—4] These diterpenes, which can be classified into three subtypes (11-membered ring, 7-membered ring, and rearranged types), have a β,β-dimethylacrylate group as a common functional moiety at the 8-position. In this communication, we report on the structures of the novel seven-membered ring vibsane-type diterpenes **1**, **2**, and **3** called aldovibsanin A, 7-epi-aldovibsanin A, and aldovibsanin B, respectively, which were isolated from the methanol extract of the leaves of *Viburnum odoratissimum* collected in Taiwan. They lack a β,β-dimethylacrylate group at the 8-position and have an additional five-membered ring on the seven-membered vibsane-type skeleton.

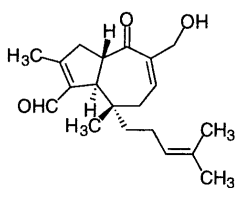
Aldovibsanin A (**1**),[5] has the molecular formula $C_{20}H_{30}O_4$ established by high-resolution (HR)-CIMS, indicating six degrees of unsaturation. The spectral data of **1** showed the presence of a hydroxyl group (3434 cm^{-1}), carbonyl groups (1715 and 1659 cm^{-1}), and an α,β-conjugated ketone (238 nm and 1659 cm^{-1}). The ^{1}H-NMR data of **1** (Table) showed the presence of an aldehyde group [δ_H 9.15 (d, J=3.6 Hz)] instead of the β,β-dimethylacrylate group which commonly exists in the vibsane-type diterpenes, as well as of four tertiary methyl groups (δ_H 0.71, 0.88, 1.56 and 1.65), two olefinic protons (δ_H 5.07 and 6.24), and an oxymethylene [δ_H 4.17 (br dd, J=13.2, 5.8 Hz), 4.25 (br dd, J=13.2, 4.4 Hz)]. Extensive analysis of ^{1}H–^{1}H correlated spectroscopy (COSY) and heteronuclear multiple quantum coherence (HMQC) gave the four partial structures **A**—**D** (Fig. 1) in addition to four quaternary carbons (δ_C 204.0, 141.7, 79.7, and 37.9). The partial structure **A** existing in the previously known vibsane-type diterpenes was not present. In order to determine the connectivities between these four partial structures and four quaternary carbons, we carried out heteronuclear multiple bond correlation (HMBC) experiments. The HMBC correlations of H-6 and H_3-19 to C-7 and H_3-19 to C-9 led to the formation of the five-membered ring containing the partial unit **A**. The other HMBC correlations, as shown by arrows in Fig. 1, allowed us to propose the plain structure **1**. The relative stereochemistry of **1** was clarified by a nuclear Overhauser exchange spectroscopy (NOESY) as shown in Fig. 2. The H-5 and H-10 showed cross peaks to H_3-20 and H-12, respectively, and thereby the five-membered ring and the seven-membered ring fused together with a *trans* relationship. The observation of cross peaks between H-10 and H-12, H-10 and H-8, and H-8 and H_3-19 indicated that both the aldehyde group at the 8-position and the methyl group at the 7-position took the same α-configurations. Thus the hydroxyl group at the 7-position turned out to be a β-configuration. Hence, on the basis of the above spectral data, the structure of aldovibsanin A was elucidated as **1**.

7-epi-Aldovibsanin A (**2**)[6] has the molecular formula $C_{20}H_{30}O_4$ as established by HR-CIMS. The spectral data of **2** were very similar to those of **1** except for the low-field shifted signal of an aldehyde group in the ^{1}H-NMR spectrum. Thus compound **2** should be an epimer of **1** with regard to C-7. Analyses of ^{1}H–^{1}H COSY, HMQC, and HMBC for **2** gave the same plain structure as **1**. The relative stereochemistry of **2** was defined by a NOESY experiment, indicating that the five-membered ring and seven-membered ring fused at *trans* in the same manner as that of **1**. The observation of cross peaks between H-9 and H_3-19, and H-8 and H-10, however, suggested that the OH group at the 7-position had an α-configuration. Thus on the basis of the above spectral data, the structure of 7-epi-aldovibsanin A (**2**) was elucidated as an epimer of **1** on the 7-position.

The ^{1}H-NMR data of aldovibsanin B (**3**)[7] were very similar to those of **1** and **2**, except for the signal of the aldehyde proton observed around 10 ppm. The molecular formula ($C_{20}H_{28}O_3$) obtained from HR-CIMS indicated that **3** was a dehydrated compound of **1** or **2**. In comparison of the ^{13}C-NMR data of **3** with those of **1** and **2**, **3** had a double bond at C-7 (δ_C 162.2) and C-9 (δ_C 137.2). Upon treatment of **1** with DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) in benzene, dehydration took place smoothly to give rise to a dehydrated compound, which was identical in all respects with **3**. Thus the structure for aldovibsanin B was determined to be **3**. Ad-



1 R_1=CH_3, R_2=OH
2 R_1=OH, R_2=CH_3



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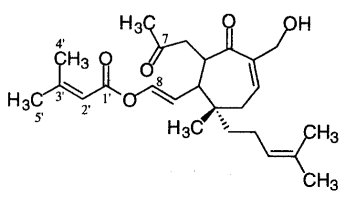

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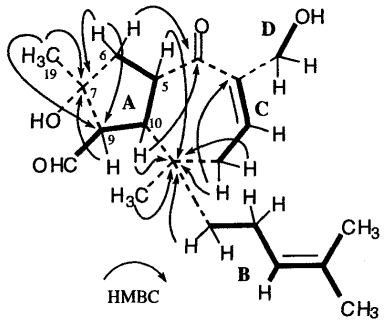

Fig. 1. HMBC of **1**

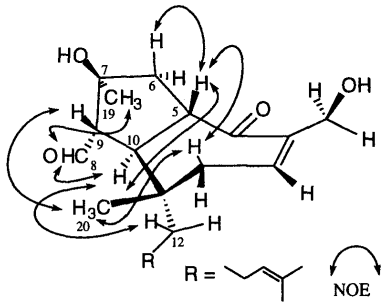

Fig. 2. NOESY of **1**

Table 1. ^{13}C and ^{1}H-NMR Data (600 MHz, C_6D_6) of **1**, **2**, and **3**

C	1		2		3	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	38.1	1.76 (dd, 14.6, 5.8) 1.89 (dd, 14.6, 5.8)	39.5	1.62 (dd, 15.1, 5.2) 1.91 (dd, 15.1, 9.6)	33.8	1.68 (br dd, 15.1, 5.2) 2.02 (dd, 15.1, 9.6)
2	139.2	6.24 (br dd, 9.6, 5.8)	139.7	6.29 (br dd, 9.6, 5.2)	141.9	6.40 (br dd, 9.6, 5.2)
3	141.7		140.8		141.8	
4	204.0		204.7		201.3	
5	52.1	2.60 (ddd, 9.9, 9.3, 8.0)	51.6	2.19 (ddd, 10.7, 9.2, 2.5)	51.3	2.45 (ddd, 9.6, 9.6)
6	42.2	1.78 (ddd, 13.5, 8.0, 1.4) 1.93 (dd,13.5, 9.3)	40.2	1.23 (dd, 14.0, 10.7) 2.49 (dd, 14.0, 2.5)	38.0	1.97 (ddq,19.2, 9.6, 0.8) 2.89 (ddq, 19.2, 9.6, 1.1)
7	79.7		82.2		162.2	
8	200.9	9.15 (d, 3.6)	208.5	9.75 (d, 4.7)	188.2	9.71 (s)
9	63.3	2.42 (ddd, 6.3, 3.6, 1.4)	62.7	2.12 (dd, 11.4, 4.7)	137.2	
10	46.4	2.45 (dd, 9.9, 6.3)	49.5	2.87 (dd, 11.4, 9.2)	54.5	2.77 (dd, 9.6, 1.9)
11	37.9		36.8		40.1	
12	42.2	1.07 (m)	41.7	1.01 (ddd, 14.0, 12.1, 5.2) 1.10 (ddd, 14.0, 11.8, 4.9)	41.4	1.75 (dd, 12.6, 3.8) 2.16 (br dd, 12.6, 3.3)
13	23.8	1.74 (m), 1.96 (m)	23.8	1.72 (dddd,12.9, 12.1, 6.9, 4.9) 1.96 (dddd, 12.9, 11.8, 9.1, 5.8)	24.5	1.98 (m), 2.11 (m)
14	124.7	5.07 (ddq, 7.1, 7.1, 1.1)	124.4	5.00 (ddq, 7.1, 6.9, 0.8)	125.4	5.35 (ddq, 6.9, 5.5, 1.3)
15	131.5		131.6		131.1	
16	17.7	1.56 (br s)	17.6	1.50 (br s)	17.8	1.69 (br s)
17	25.8	1.65 (br d, 1.1)	25.7	1.61 (d, 0.8)	25.9	1.70 (br s)
18	63.9	4.17 (br dd, 13.2, 5.8) 4.25 (br dd, 13.2, 4.4)	64.0	4.20 (br d, 13.2) 4.29 (br d, 13.2)	63.9	4.20 (br d, 13.2) 4.29 (br d, 13.2)
19	24.9	0.88 (s)	26.1	1.04 (s)	14.5	1.42 (ddd, 1.9, 1.1, 0.8)
20	23.7	0.71 (s)	23.6	0.52 (s)	22.9	0.60 (s)

ditionally, the CD spectrum of **3** showed the same negative Cotton effect as that of the compound[4] which was obtained from vibsanin C (**4**) by hydrolysis with 2 N NaOH. Thus the absolute configurations of **1**—**3** were determined to be 5*S*, 10*S*, and 11*S* respectively. In brine shrimp assay,[8] aldovibsanin B showed a weak lethal activity (LD_{50}=76 ppm), implying cytotoxic activity. Since some vibsane-type diterpenes exhibit cytotoxic activity,[9] aldovibsanin B (**3**) will be evaluated by cytotoxic tests using human cancer cell lines.

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References and Notes

1) Minami H., Anzaki S., Kubo M., Kodama M., Kawazu K., Fukuyama Y., *Chem. Pharm. Bull.*, **46**, 1194—1198 (1998).
2) Fukuyama Y., Minami H., Takauchi K., Kodama M., Kawazu K., *Tetrahedron Lett.*, **37**, 6767—6770 (1996).
3) Fukuyama Y., Minami H., Yamamoto I., Kodama M., Kawazu K., *Chem. Pharm. Bull.*, **46**, 545—547 (1998).
4) Fukuyama Y., Minami H., Takaoka S., Kodama M., Kawazu K., Nemoto H., *Tetrahedron Lett.*, **38**, 1435—1438 (1997).
5) **1**: $[\alpha]_D^{24}$ +95.0° (*c* 0.52, $CHCl_3$); HR-CIMS *m/z*: 334.2155 (calcd for $C_{20}H_{30}O_4$; found 334.2144); IR (FT) cm^{-1}: 3434 (OH), 1659, 1715 (C=O); UV λ_{max}^{EtOH} nm: 238 (ε 7136).
6) **2**: $[\alpha]_D^{24}$ +95.0° (*c* 0.46, $CHCl_3$); HR-CIMS *m/z*: 334.2146 (calcd for $C_{20}H_{30}O_4$; found 334.2144); IR (FT) cm^{-1}: 3409 (OH), 1659, 1715 (C=O); UV λ_{max}^{EtOH} nm: 237 (ε 6245).
7) **3**: $[\alpha]_D^{23}$ −8.2° (*c* 0.40, $CHCl_3$); HR-CIMS *m/z*: 316.2065 (calcd for $C_{20}H_{28}O_3$; found 316.2038); IR (FT) cm^{-1}: 3422 (OH), 1669 (C=O); UV λ_{max}^{EtOH} nm: 237 (ε 7388).
8) Meyer B. N., Ferrigi N. R., Putnam J. E., Jacobsen L. B., Nichols D. E., McLaughlin J. L., *Planta Med.*, **45**, 31—34 (1982).
9) Fukuyama Y., Minami H., Anzaki S., Takeuchi K., Yasutomi S., Kodama M., Kawazu K., Nemoto H., Abstracts of Papers, The 38th Symposium on the Chemistry of Natural Products, 103—108 (1996).