

Chemical Conversion of Vibsantin C to Vibsantin E and Structure of 3-Hydroxyvibsantin E from *Viburnum awabuki*

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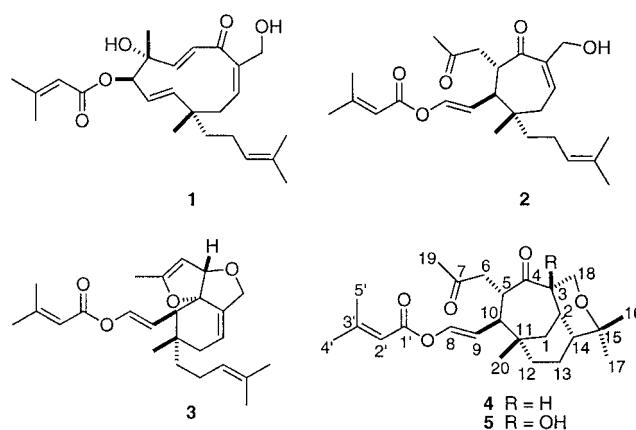
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Vibsantin E (**4**), a tricyclic vibsane-type diterpene, has been prepared in 50% yield from vibsantin C (**2**), a seven-membered ring vibsane-type diterpene by reaction with $\text{BF}_3 \cdot \text{OEt}_2$ at -78°C . This chemical correlation not only established structure, including absolute configurations, but also has demonstrated a possible biosynthetic route to **4** via **2** derived from vibsantin B (**1**). The structure of 3-hydroxyvibsantin E (**5**), another example of a tricyclic seven-membered ring vibsane, isolated from the leaves of *Viburnum awabuki*, has been established by extensive analyses of 2D NMR data and comparison of its spectral data with those of **4**.

Vibsane-type diterpenes,¹ which consist of a fumulane-type carbon skeleton with an additional isoprene unit, are very rare in nature. Their occurrence had been limited to the genus *Viburnum* (Caprifoliaceae)² until some examples of *ent*-vibsane-type diterpenes were isolated from the liverwort *Odontoschisma denudantum*.³ The carbon skeletons of vibsane-type diterpenes can be classified into three subgroups characterized by an eleven-membered ring, a seven-membered ring, and a rearranged type and are represented by vibsantin B (**1**), vibsantin C (**2**),⁴ and neovibsantin (**3**),⁵ respectively. In previous papers,^{1,5} we successfully correlated **1** to **2** and **3** by thermal and photochemical reactions, respectively, and thereby not only established their absolute configurations but also suggested a plausible biosynthesis for the three subtypes of vibsane-type diterpenes. Another vibsane-type diterpene, vibsantin E (**4**), was isolated from *V. awabuki* by K. Kawazu, and its absolute structure was unambiguously established by X-ray crystallographic analysis.⁶ One assumes that the unique tricyclic structure of **4** must be formed somehow from **2**, but a chemical method to construct the tricyclic system in **4** had not been achieved. In this paper, we report the successful chemical conversion of **2** to **4** and the structure elucidation of a new diterpene, 3-hydroxyvibsantin E (**5**), isolated from the leaves of *V. awabuki*. The leaves of *V. awabuki* K. Koch (Caprifoliaceae) were extracted with MeOH, and the evaporated extract was purified by repeated chromatography on Si gel to yield **4** and **5**.

The initial attempts to convert **2** to **4** were unsuccessful. Although treatment of **2** with acids was found to give some tricyclic products, the acid-sensitive enol ester group in **2** caused side reactions and yielded no product corresponding to **4**. After several efforts failed, we found that when **2** was treated with boron trifluoride diethyl etherate in CH_2Cl_2 under anhydrous conditions at -78°C for a short period, it gave **4** in 50% yield.

Compound **5** was obtained as a colorless, amorphous solid. Its FABMS exhibited quasi-molecular ion peaks at m/z 433 and 455, and the molecular formula $\text{C}_{25}\text{H}_{36}\text{O}_6$, consistent with eight unsaturation units, was assigned by HRFABMS. Absorption bands in the IR (3461, 1728, and 1710 cm^{-1}) and UV (230 nm) spectra of **5** suggested the



presence of a hydroxyl, carbonyl, and conjugated ester groups. The ^1H and ^{13}C NMR data (Table 1) of **5** showed the presence of six tertiary methyl groups (δ 0.82, 1.13, 1.18, 1.37, 1.38, and 2.05), an isolated oxymethylene (δ 3.66, 4.36; δ 65.9), a trisubstituted olefin (δ 5.70; δ 115.0, 160.0), and a disubstituted olefin (δ 4.99, 7.28; δ 115.8, 135.2). These data were very similar to those of **4**. Comparison of the NMR data (Table 1) of **5** and **4** indicated that **5** had the hydroxy group at the C-3 position in **4**. This hydroxyl proton signal, which was assigned to δ 4.91 (s), showed distinct HMBC correlations to C-2, C-3, C-4, and C-18, thereby supporting its position on C-3. The other partial structures obtained by 2D COSY and HMQC and their assembly made up by HMBC as shown in Table 1 indicated that **5** is 3-hydroxyvibsantin E. The relative stereochemistry for **5** was assigned to be the same as that of **4** on the basis of cross peaks as shown in Figure 1 on 2D NOESY. The CD spectrum of compound **5** displayed the same positive Cotton effect as that of **4**. Therefore, 3-hydroxyvibsantin E (**5**) had 3*S*, 5*S*, 10*R*, and 11*S* configurations.

The present study has demonstrated that vibsantin E (**4**), the first example of a tricyclic seven-membered ring vibsane, can be derived from the seven-membered ring vibsane, vibsantin C (**2**) by a cationic process and has established that **4** has the same absolute configuration as **2**. From a biosynthetic point of view, **4** may be formed in the plant from **2** available from the eleven-membered ring vibsane, vibsantin B (**1**). 3-Hydroxyvibsantin (**5**) is the second example of a tricyclic seven-membered ring vibsane. This structural diversity of the vibsane-type diterpenes encour-

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Table 1. NMR Spectra Data of Compounds **4** and **5** in C₆H₆-d₆ (600 MHz for ¹H NMR, 150 MHz for ¹³C NMR)

position	4		5		HMBC Correlations ^c
	δ_{H}^a	δ_{C}^b	δ_{H}^a	δ_{C}^b	
1	1.10 (dd, 14.8, 5.5) 2.00 (br d, 14.8)	41.3	1.03 (dd, 14.8, 5.5) 2.68 (dd, 14.8, 2.1)	36.6	C-2, C-3, C-10, C-11, C-2, C-11, C-12, C-14
2	2.13 (m)	29.8	2.41 (ddd, 5.5, 4.4, 2.5)	37.1	C-3, C-4, C-11, C-14, C-15
3	2.26 (dd, 7.7, 3.3)	50.1		74.4	
4		212.9		213.8	
5	3.06 (ddd, 11.5, 10.7, 3.0)	47.7	3.43 (ddd, 11.8, 11.8, 3.0)	43.1	C-10
6	2.13 (dd, 17.6, 3.0) 2.98 (dd, 17.6, 10.7)	46.1	2.01 (dd, 19.0, 3.0) 2.91 (dd, 19.0, 11.8)	46.4	C-4, C-7, C-10 C-4, C-7, C-10
7		206.9		210.8	
8	7.25 (d, 12.4)	135.1	7.28 (d, 12.4)	135.2	C-1', C-9, C-10
9	5.09 (dd, 12.4, 11.8)	116.3	4.99 (dd, 12.4, 11.8)	115.8	C-8
10	1.72 (dd, 11.8, 11.5)	46.0	1.68 (t, 11.8)	45.7	C-4, C-5, C-8, C-9, C-11, C-12
11		34.9		35.3	
12	0.76 (ddd, 14.1, 14.1, 3.3) 1.25 (m)	42.4	0.77 (m) 1.25 (m)	42.0	
13	1.16 (m), 1.25 (m)	19.1	1.16 (m), 1.29 (m)	19.3	C-14
14	0.67 (ddd, 12.6, 4.4, 4.1)	43.4	0.92 (ddd, 13.2, 4.4, 4.4)	43.9	
15		72.5		72.7	
16	1.11 (s)	23.3	1.18 (s)	23.5	C-14, C-15, C-17
17	1.04 (s)	28.3	1.13 (s)	27.8	C-14, C-15, C-16
18	3.32 (dd, 11.8, 3.3) 4.48 (d, 11.8)	59.2	3.66 (d, 11.4) 4.36 (d, 11.4)	65.9	C-2, C-3, C-4, C-15 C-3, C-4
19	1.62 (s)	29.5	1.38 (s)	28.9	C-6, C-7
20	0.79 (s)	31.9	0.82 (s)	31.7	C-1, C-10, C-11, C-12
1'		163.2		163.2	
2'	5.69 (qq, 1.1, 1.1)	115.1	5.70 (qq, 1.1, 1.1)	115.0	C-4', C-5'
3'		159.8		160.0	
4'	1.37 (d, 1.1)	20.3	1.37 (d, 1.1)	20.3	C-2', C-3', C-5'
5	2.06 (d, 1.1)	27.3	2.05 (d, 1.1)	27.0	C-2', C-3', C-4'
C ₃ -OH			4.91 (s)		C-2, C-3, C-4, C-18

^a Chemical shift (δ) in ppm from TMS, multiplicities, and coupling constants in Hz are in parentheses. ^b Chemical shift (δ) in ppm from TMS. ^c Correlations from H to the indicated carbons.

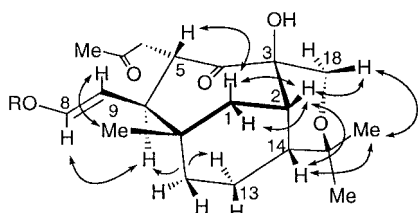


Figure 1. Relative stereochemistry for **5** based on NOESY. Arrows indicate NOE correlations.

ages us to continue studying the chemical components of *Viburnum* species.

Experimental Section

General Experimental Procedures. Melting points were determined with a Mitamura hot-stage microscope and are uncorrected. IR and UV spectra were obtained using a JASCO FTIR-5300 and a Shimadzu UV-300 spectrophotometer, respectively. NMR spectra were recorded on a Varian Unity 600 and 200, with TMS as the internal standard. The HMBC, HMQC, and ROESY were run on a Varian Unity at 600 MHz. MS were measured with a JEOL JMS AX-500. CD spectra were recorded on a JASCO J-500. Si gel 60 (Merck) and Wako gel C-300 (Wako) were used for column chromatography. Analytical TLC was carried out on Si gel plates (Kieselgel 60, Merck) and visualized by 5% CeSO₄ in H₂SO₄ followed by heating.

Plant Material. The leaves of *Viburnum awabuki* were collected in Tokushima, Japan. A voucher specimen (1315LF) has been deposited at the Institute of Pharmacognosy, Tokushima Bunri University.

Extraction and Isolation. The dried and powdered leaves of *V. awabuki* (1.5 kg) were immersed in MeOH at room temperature for 1 month. The MeOH extract was evaporated in vacuo to give a gummy extract (500 g). The extract (20 g) was subjected to a Si gel (Merck) column chromatography eluted, in order, with hexane (100%), hexane-EtOAc (7:3),

hexane-EtOAc (1:1), EtOAc (100%), EtOAc-MeOH (8:2), and MeOH (100%), yielding 10 fractions. Fraction 5 (4.9 g) was rechromatographed on Si gel (Wako) with CHCl₃-EtOAc (5:1) to give fractions 11-16. Fraction 13 (1.12 g) was subjected to reversed-phase chromatography using Cosmosil 75C18-OPN and eluted with MeOH-H₂O (5:1) to give fractions 17-19. Fraction 18 (66 mg) was purified by Si gel chromatography with hexane-EtOAc (2:1) to afford vibsananin E (**4**) (11.1 mg) and 3-hydroxyvibsananin E (**5**) (12.8 mg).

Vibsananin E (4): colorless prisms, mp 147-148 °C; [α]_D²¹ -61° (c 0.3, CHCl₃); IR (CHCl₃) 1732, 1647 cm⁻¹; UV λ_{max} (EtOH) 230 (ϵ 13 700) nm; CD (EtOH) $\Delta\epsilon_{275}$ +15.2; ¹H and ¹³C NMR, see Table 1; FABMS *m/z* 439 [M + Na]⁺, 417 [M + H]⁺; HRFABMS *m/z* 439.2468 [M + Na]⁺ (calcd for C₂₅H₃₆O₅Na, 439.2461).

3-Hydroxyvibsananin E (5): colorless amorphous solid; [α]_D²¹ +6.3° (c 0.3, EtOH); IR (neat) 3461, 1728, 1710 cm⁻¹; UV λ_{max} (EtOH) 230 (ϵ 10 000) nm; CD (EtOH) $\Delta\epsilon_{278}$ +15.7; ¹H and ¹³C NMR, see Table 1; FABMS *m/z* 455 [M + Na]⁺, 433 [M + 1]⁺; HRFABMS *m/z* 455.2443 [M + Na]⁺ (calcd for C₂₅H₃₆O₆Na, 455.2410).

Conversion of Vibsananin C (2) to Vibsananin E (4): To a solution of vibsananin C (**2**) (8 mg) in CH₂Cl₂ (0.5 mL) was added boron trifluoride diethyl etherate (0.025 mL) at -78 °C. After being stirred for 18 min, the mixture was diluted with a saturated aqueous solution of NaHCO₃ and extracted with Et₂O and washed with H₂O and brine, then dried over MgSO₄. The solvent was removed in vacuo to give a crude oil, which was purified by HPLC [Cosmosil 5C18 AR, ϕ 10 × 250 mm; solvent: MeOH-MeCN-H₂O (3:1:1.5), 2 mL/min] to yield vibsananin E (**4**) (4 mg, 50%) as colorless prisms: 147-148 °C; [α]_D²¹ -65° (c 0.3, CHCl₃). All spectral data of synthetic **4** were identical with those of the natural product isolated from *V. awabuki*.

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