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Absolute Structure of Vibsanins B and C, and Their Chemical Correlation

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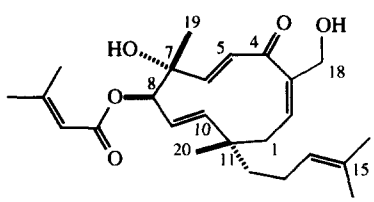
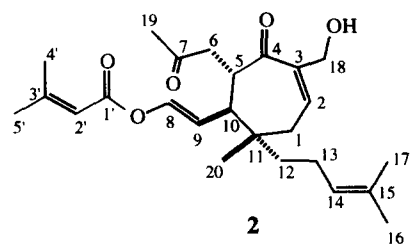
Abstract: The absolute structure of vibsanin C, a novel 7-membered vibsane-type diterpene isolated from the leaves of *Viburnum awabuki*, has been established by X-ray crystallographic analysis of its derivative. Vibsanin C has been proved to be one of Cope rearranged products from vibsanin B, a 11-membered vibsane-type diterpene.

In the course of our search for biologically active substances in the methanol extract of the leaves of *Viburnum awabuki*,[1] we have been successful in isolating a number of novel cytotoxic vibsane-type diterpenes[2,3] together with the previously reported vibsanins A ~ E.[4,5] Carbon skeletons of these vibsane-type diterpenes can classify into three types of 11-membered, 7-membered and rearranged ones, which are represented by vibsanin B (**1**), vibsanin C (**2**) and neovibsanins,[2] respectively. Although vibsanins A ~ E were conceived to belong to unprecedented diterpenoids, their relative and absolute configurations except for vibsanin E,[5] however, have remained undefined. It is essentially indispensable for a structural study on new vibsane-type diterpenes to unambiguously assign the stereochemistry of the known vibsanes. Hence, we have decided to establish the absolute structure of vibsanins B (**1**) and C (**2**), typical 11- and 7-membered vibsanes. In this paper, we wish to report the complete structure of vibsanins B (**1**) and C (**2**), and thermal conversion of **1** into 7-membered vibsanins including **2** by a Cope rearrangement.

All the ^{1}H NMR ($CDCl_3$) signals of **1** appeared as pairs of 4 : 1 ratio, which had cross peaks to each other due to a saturation transfer in addition to normal cross peaks in the NOESY experiment done at 24 °C. This suggests that **1** exits in a mixture of two conformers in $CDCl_3$ solution.[6] The relative stereochemistry for two conformers **1a** and **1b**[7] was elucidated on the basis of NOE data as shown in Fig.1 as well as of $J_{8,9}$ value[8] (**1a**:



1



2

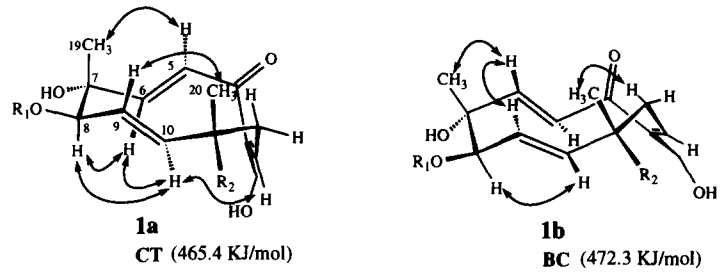


Fig. 1. Two conformers **1a** and **1b** elucidated by NOESY, and the lowest energy conformers **CT** and **BC** obtained by MM2 calculation. The arrows show the NOE relationships.

9.3 Hz; **1b**: 2.2 Hz). The main conformer **1a** adopts a chair conformation at C-5 ~ C-10 and takes a *transoid* geometry for an α, β-unsaturated ketone at C-4 ~ C-6, whereas the minor one **1b** consists of a boat conformation and a *cisoid* form at the positions corresponding to those of **1a** , respectively. In order to know the most stable conformation of **1**, molecular mechanics calculations were performed using the MM2 force field as implemented in MacroModel/Batchmin (Ver 4.5). The starting geometries were generated by a systematic Monte Carlo conformational search. Two most stable conformers **CT** and **BC**[9] found within 1.8 kcal/mol of the global minimum energy were consistent with **1a** and **1b** elucidated by NOE data, respectively.

In course of VT experiments of **1** in DMSO-d_6, we found that **1** induced an irreversible change at 110 °C. So, this thermal transformation of **1** was examined in full detail. A solution of **1** in toluene was refluxed for 1 h to afford four products, which were separated by HPLC giving rise to **2** (85.9 %), **2a** (11.2 %), **2b** (1.6 %) and **2c** (0.2 %).[10] Their relative structures as shown in Fig. 2 were unambiguously determined by extensive spectroscopic analyses (Table 1). Among four compounds, the major product **2** was identical in all respects with vibsanin C. The formation of **2**, **2a**, **2b** and **2c** can be ascribed to a Cope rearrangement of **1**. Vibsanin B (**1**) is explicable to thermally rearrange through the **CT** and **BC** conformers into vibsanin C (**2**) and product **2b** which have a $\Delta^{8,9}$ *E* olefin, but not into products **2a** and **2c** bearing a $\Delta^{8,9}$ *Z* olefin. Search for suitable conformers leading to **2a** and **2c** resulted in the discovery of two **CC** (491.1 KJ/mol) and **BT** (483.4 KJ/mol) conformers existed within 6 kcal/mol of the global minimum energy. Although we have defined no concrete transition state in a Cope rearrangement of **1**, **CC** and **BT** may be putative conformations through which **1** could be transformed to **2a** and **2c**, respectively, since both of the conformers can rationalize not only the stereochemistry at the C-5 and C-10 positions (**2a**: 5*R**, 10*S**; **2c**: 5*S**, 10*S**) but also a $\Delta^{8,9}$ *Z* geometry of **2a**

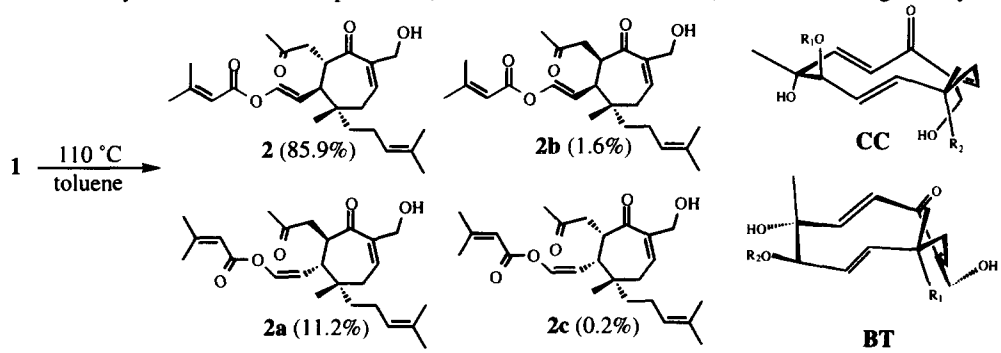


Fig. 2. The products **2**, **2a**, **2b** and **2c** obtained from **1** via a Cope rearrangement, and **CC** and **BT** conformers leading to **2a** and **2c**, respectively.

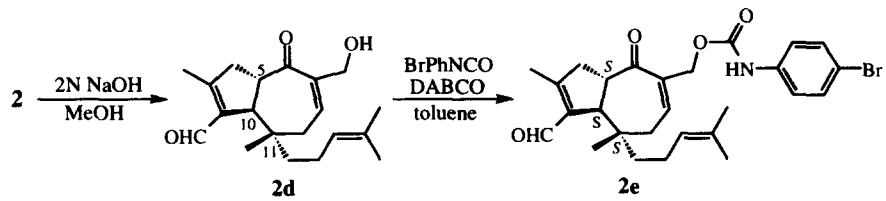
Table 1. ^{1}H and ^{13}C NMR data for **2**, **2a**, **2b** and **2c** in $CDCl_3$

	2		**2a**		**2b**		**2c**	
C	δ_H[a]	δ_C[b]	δ_H[a]	δ_C[b]	δ_H[a]	δ_C[b]	δ_H[c]	δ_C[d]
1	1.82 (*dd*, 15.1, 8.8,) 1.91 (*dd*, 15.1, 5.1)	35.9	1.76 (*dd*, 15.1, 8.8) 1.95 (*dd*, 15.1, 5.4)	36.3	1.92 (*dd*, 16.1, 7.6) 2.01 (*dd*, 16.1, 5.4)	38.7	1.92 (2H, *d*, 6.0)	35.8
2	6.16 (*dd*, 8.8, 5.1)	137.7	6.12 (*dd*, 8.8, 5.4)	135.7	6.13 (*dd*, 7.6, 5.4)	138.6	6.10 (*t*, 6.0)	137.8
3		142.9		143.9		143.9		143.4
4		205.1		206.1		203.7		203.9
5	2.90 (*ddd*, 9.8, 6.8, 4.6)	48.4	2.75 (*ddd*, 9.8, 7.1, 2.7)	48.4	3.52 (*ddd*, 9.3, 4.6, 4.4)	48.3	3.58 (*ddd*, 7.7, 5.4, 4.1)	47.9
6	2.51 (*dd*, 17.6, 4.6) 2.78 (*dd*, 17.6, 6.8)	44.2	2.58 (*dd*, 16.4, 2.7) 2.79 (*dd*, 16.4, 7.1)	44.2	1.83 (*dd*, 17.8, 4.6) 3.05 (*dd*, 17.8, 9.3)	44.3	2.12 (*dd*, 18.1, 5.4) 3.04 (*dd*, 18.1, 7.7)	44.8
7		206.4		206.4		205.7		205.9
8	7.18 (*d*, 12.2)	136.8	7.29 (*d*, 6.6)	135.6	7.38 (*d*, 12.5)	137.7	7.34 (*d*, 6.6)	136.9
9	5.15 (*dd*, 12.2, 11.5)	113.4	4.29 (*dd*, 11.2, 6.6)	112.1	5.33 (*dd*, 12.5, 11.7)	111.7	4.45 (*dd*, 11.5, 6.6)	110.6
10	2.13 (*dd*, 11.5, 9.8)	46.3	3.13 (*dd*, 11.2, 9.8)	43.4	2.01 (*dd*, 11.7, 4.4)	47.7	2.95 (*dd*, 11.5, 4.1)	43.6
11		40.1		39.6		42.7		40.4
12	1.19 (2H, *m*)	40.0	1.22 (2H, *m*)	38.8	1.31 (*m*) 1.46 (*m*)	40.5	1.13 (*ddd*, 13.5, 13.5, 4.9) 1.21 (*ddd*, 13.5, 11.5, 4.4)	39.3
13	1.77 (2H, *m*)	23.3	1.87 (2H, *m*)	22.7	1.92 (2H, *m*)	22.7	1.83 (*m*), 1.91 (m)	23.0
14	5.07 (*t*, 7.0)	124.9	5.18 (*t*, 7.8)	125.2	5.17 (*t*, 7.2)	124.9	5.11 (*t*, 7.0)	125.0
15		131.2		131.2		131.4		131.2
16	1.54 (3H, *s*)	17.6	1.59 (3H, *s*)	17.7	1.63 (3H, *d*, 0.7)	17.7	1.54 (3H, *s*)	17.5
17	1.63 (3H, *s*)	25.7	1.71 (3H, *s*)	25.8	1.70 (3H, *d*, 0.7)	25.8	1.62 (3H, *s*)	25.8
18	4.31 (*d*, 12.9) 4.38 (*d*, 12.9)	63.7	4.34 (*d*, 12.7) 4.47 (*d*, 12.7)	63.9	4.21 (*d*, 13.2) 4.30 (*d*, 13.2)	64.2	4.22 (*d*, 13.2) 4.28 (*d*, 13.2)	64.7
19	1.78 (3H, *s*)	29.5	1.71 (3H, *s*)	29.3	1.74 (3H, *s*)	29.7	1.73 (3H, *s*)	29.7
20	0.69 (3H, *s*)	24.0	0.89 (3H, *s*)	25.0	0.67 (3H, *s*)	24.6	1.07 (3H, *s*)	26.2
1'		163.1		163.1		163.2		162.7
2'	5.63 (*qq*, 1.2, 1.2)	114.9	5.67 (*qq*, 1.2, 1.2)	115.1	5.62 (*qq*, 1.2, 1.2)	115.0	5.64 (*qq*, 1.1, 1.1)	114.8
3'		160.0		160.1		160.1		160.4
4'	2.02 (3H, *d*, 1.2)	20.2	2.02 (3H, *d*, 1.2)	20.4	2.01 (3H, *d*, 1.2)	20.2	2.20 (3H, *d*, 1.1)	20.3
5'	1.37 (3H, *d*, 1.2)	27.0	1.31 (3H, *d*, 1.2)	27.0	1.36 (3H, *d*, 1.2)	27.0	1.37 (3H, *d*, 1.1)	27.0

[a] 400 MHz. [b] 100 MHz. [c] 600 MHz. [d] 150 MHz.

and **2c**. Thus, 11-membered vibsanin B (**1**) was thermochemically correlated to 7-membered vibsanin C (**2**) as well as to its possible stereoisomers **2a** ~ **2c** which have not been so far found in natural product.

Next, our attention focused on the absolute configuration of vibsanin C (**2**), which has been completely correlated with vibsanin B (**1**) via a Cope rearrangement. The enol ester of **2** was saponified with 2N NaOH in MeOH, followed by an intramolecular aldol condensation, to furnish the aldehyde **2d**. The *p*-bromophenyl carbamate derivative **2e**[11] of **2d** gave a single crystal suitable for X-ray analysis. A total of 1597 refractions was used for the structure analysis. The structure was solved by direct method using the CRYSTAN SIR92[12] (MacScience). The final R value was 0.059. The absolute configuration of the molecule as shown in Fig. 3



2d **2e**

was determined by η value (0.971).[13] According to the absolute configuration of **2e**, vibsanin C (**2**)[14] consists of 5*S*, 10*R* and 11*S*, and thereby vibsanin B (**1**) must have the chiral centers of 7*R*, 8*R* and 11*S*.

In conclusion, we have established the absolute structures of typical vibsane-type diterpenoids, vibsanins B (**1**) and C (**2**), which have been verified to be biogenetically correlated to each other through Cope-like rearrangement. Additionally, the above result implies that stereoisomers of vibsanin C may occur in natural product. With these data in mind, we are now continuing study on structure and biological property of new vibsane-type diterpenes isolated from *V. awabuki*. These results will be reported in due time.

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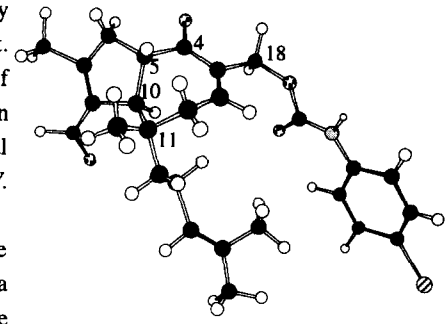

Fig. 3. ORTEP drawing of the molecular structure of **2e**

References and Notes

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4. Kawazu, K.; *Agric. Biol. Chem.* **1980**, 44, 1367.
5. Fukuyama, K.; Katsube, Y.; Kawazu, K.; *J. Chem. Soc. Perkin II*, **1980**, 1701.
6. In the other solvents (C_6D_6 and DMSO-d_6), pairs of signals due to two conformers were observed at 24 °C.
7. **1a**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.98 (3H, s, H_3-20), 1.30 (2H, m, H-12), 1.35 (3H, s, H_3-19), 1.55 (3H, s, H_3-17), 1.66 (3H, s, H_3-16), 1.76 (1H, m, H-13), 1.77 (1H, dd, *J* = 13.4, 12.8 Hz, H-1), 1.89 (3H, d, *J* = 1.0 Hz, H-5'), 1.93 (1H, m, H-13), 1.99 (1H, dd, *J* = 13.4, 4.0 Hz, H-1), 2.14 (3H, d, *J* = 1.0 Hz, H_3-4'), 4.01 (1H, d, *J* = 11.2 Hz, H-18), 4.39 (1H, d, *J* = 11.2 Hz, H-18), 5.07 (1H, t, *J* = 7.0 Hz, H-14), 5.11 (1H, dd, *J* = 16.1, 9.3 Hz, H-9), 5.34 (1H, d, *J* = 9.3 Hz, H-8), 5.72 (1H, d, *J* = 16.1 Hz, H-10), 5.74 (1H, qq, *J* = 1.0, 1.0 Hz, H-2'), 5.91 (1H, dd, *J* = 12.8, 4.0 Hz, H-2), 6.06 (1H, d, *J* = 16.4 Hz, H-5), 6.65 (1H, d, *J* = 16.4 Hz, H-6). **1b**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.09 (3H, s, H_3-20), 1.24 (2H, m, H-12), 1.29 (3H, s, H_3-19) , 1.52 (3H, s, H_3-17), 1.63 (3H, s, H_3-16), 1.84 (2H, m, H-13), 1.94 (2H, m, H-1), 1.94 (3H, s, H_3-5'), 2.18 (3H, s, H_3-4'), 4.13 (1H, d, *J* = 11.7 Hz, H-18), 4.43 (1H, d, *J* = 11.7 Hz, H-18), 5.01 (1H, m, H-14), 5.26 (1H, d, *J* = 2.2 Hz, H-8), 5.43 (1H, d, *J* = 16.6 Hz, H-10), 5.57 (1H, dd, *J* = 16.6, 2.2 Hz, H-9), 5.83 (1H, brs, H-2'), 6.00 (1H, dd, *J* = 12.5, 4.1 Hz, H-2), 6.25 (1H, d , *J* = 15.9 Hz, H-5), 6.71 (1H, d, *J* = 15.9 Hz, H-6).
8. *J* values between H-8 and H-9 seem to be consistent with dihedral angles (**1a**: $\phi \cong 170°$; **1b**: $\phi \cong 130°$) between the C-9 vinyl and C-8 allylic carbon-hydrogen bonds in the two conformers elucidated by NOEs. Garbisch, Jr. E. W.; *J. Am. Chem. Soc.*, **1964**, 86, 5561.
9. **CT**: chair for C5~C10 and transoid for C4~C6; **BC**: boat for C5~C10 and cisoid for C4~C6.
10. **2**: $[\alpha]_D^{23}$ +142.4° (c 0.95, $CHCl_3$); CD Δε (267 nm) +3.4. **2a**: $[\alpha]_D^{23}$ -20.7° (c 0.22, $CHCl_3$). **2b**: $[\alpha]_D^{23}$ +38.6° (c 0.59, $CHCl_3$). **2c**: $[\alpha]_D^{23}$ +62.7° (c 0.15, $CHCl_3$). **2c** should be vibsanin D[4] in comparison with specific rotation.
11. **2e**: mp 108 – 110 °C (*n*-hexane–EtOH). Crystal data: $C_{27}H_{32}O_4NBr$; monoclinic; space group $P2_1$; a = 16.127 (4), b = 10.745 (3), c = 15.575 (4) Å, β = 107.67°; Dx = 1.327mgm^{-3}; z = 4; μ(CuKα) = 24.282 mm^{-1}.
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14. All the chiral centers on **2** are the same as those corresponding to vibsanin E.[5]

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