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Novel *ent*-Vibsane- and Dolabellane-type Diterpenoids from the Liverwort *Odontoschisma denudatum*

Toshihiro Hashimoto, Masao Toyota, Hiroki Koyama, Akari Kikkawa, Mayumi Yoshida, Masami Tanaka, Shigeru Takaoka and Yoshinori Asakawa *

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan

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Abstract: From the ether extract of the liverwort *Odontoschisma denudatum*, three novel *ent*-bibsane- and a novel dolabellane-type diterpenoids have been isolated. Their absolute structures were determined by a combination of 2D-NMR, X-ray crystallographic analysis, modified Mosher method, and chemical degradation. © 1998 Elsevier Science Ltd. All rights reserved.

Liverworts contain both terpenoids and aromatic compounds which constitute the oil bodies. We have reported the distribution of a number of new terpenoids and aromatic compounds in more than 200 species of liverworts.[1, 2] Previously, Matsuo reported the isolation and structure elucidation of five new dollabelane-type diterpenoids from the liverwort *Odontoschisma denudatum*.[3] In pursuit of pharmacologically interesting substances found in liverworts, we have reinvestigated chemical constituents of the Et_2O extract of *O. denudatum*, and isolated three novel *ent*-vibsane-type diterpenoids named denudatenones A~C (**1~3**) and a new dolabellane-type diterpenoid (**4**). Here we wish to report the isolation and structure elucidation of **1~4.**

The ether extract (32.7 g) of dry material (1.25 kg) of *O. denudatum* collected in Tokushima in 1996 was subjected repeatedly to column chromatography on Sephadex LH-20 ($CHCl_3$:MeOH=1:1) and silica gel (*n*-hexane-AcOEt, gradient) followed by HPLC (Chemco sorb 5Si-U; 3% AcOEt-CH_2Cl_2) to afford denudatenone A (**1**)[4] (0.49 g), B (**2**)[5] (1.25g), C (**3**)[6] (1.05g), and acetoxyodontoschismenetriol (**4**)[7] (1.36 g).

The FT-IR spectrum of denudatenone A (**1**) ($C_{20}H_{30}O_2$) indicated the presence of a hydroxyl group (3402 cm^{-1}) and a carbonyl (1711 cm^{-1}) group. The ^1H and ^{13}C NMR spectra of **1** showed the presence of a tertiary methyl [δ_H 1.04 (3H, *s*)], two secondary methyl [δ_H 1.07, 1.08 (each 3H, *d*, *J*= 7.1Hz)], two vinyl methyls [δ_H 1.43, 1.75 (each 3H, *br. s*)], two three-substituted olefines [δ_H 4.99 (*br. d*, *J*=9.9 Hz), 5.03 (*dd*, *J*=3.6, 9.6 Hz)], a two-substituted *trans*-olefine [δ_H 5.03 (*dd*, *J*=1.1, 16.2 Hz), 5.63 (*ddd*, *J*=6.9, 7.7, 16.2 Hz)], a carbonyl group [δ_C 215.2 (*s*)] and a secondary alcohol [δ_H 4.53 (*ddd*, *J*=5.5, 9.9, 9.9 Hz)] which was confirmed by the formation of a monoacetate **5** [δ 2.03 (3H, s)] on acetylation with Ac_2O and pyridine. The stereostructure of **1** was deduced from careful analysis of HMBC (Figure 1) and NOESY spectra of **1**, and finally established by X-ray crystallography[8] of a 3, 5-dinitrobenzoate **6** of **1** as shown in Figure 2. The absolute configuration of **1** was elucidated by two experimental results described below. Compound **1** was treated with *p*-bromobenzoyl chloride and DMAP in pyridine to give the *p*-bromobenzoate **7**. The CD spectrum of **7** showed a negative first Cotton effect at 251 nm (Δε -10.6) and a positive second Cotton effect at 212 nm (Δε +56.0). Compound **1** was esterified with (+)- and (-)-MTPA, DCC and DMAP in CH_2Cl_2 to afford the (-)-MTPA ester (**8**) and the (+)-MTPA ester (**9**), respectively. The Δδ values [$\delta_{(-)}$-$\delta_{(+)}$] are shown in Figure 3 indicating that the absolute

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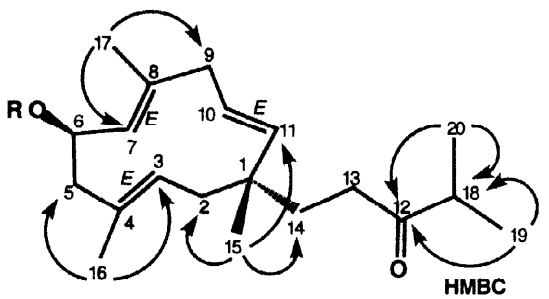
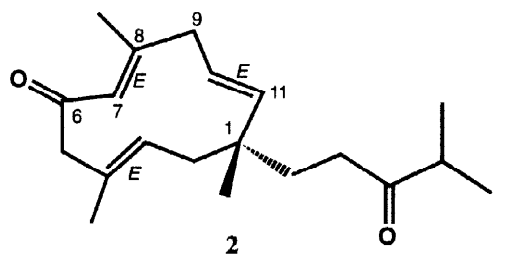
configuration of C-5 of **1** was represented as *R* by modified Mosher method.[9] The absolute configuration of denudatenone A was thus determined as **1**.

The IR and UV spectrum of denudatenone B (**2**) ($C_{20}H_{32}O_2$) indicated the presence of a carbonyl group (1711 cm^{-1}) and an α, β-unsaturated carbonyl [1692 cm^{-1}; λ_{max} 243 nm (log ε 3.72)] group. The ^1H and ^{13}C NMR spectra of **2** were quite similar to those of denudatenone A (**1**) except for the observation of a carbonyl signal [δ_C 200.3 (*s*)] at C-5 instead of the methine proton at H-5 of **1**, suggesting that **2** was the 5-oxo-compound of **1**. Swern oxidation [$(COCl)_2$/DMSO/Et_3N] of **1** gave **2** in 88.7 % yield; hence, the absolute structure of denudatenone B (**2**) was determined as the 5-oxo-compound of denudatenone A (**1**).



1 : R=H
5 : R=Ac
6 : R=3,5-Di-NO_2-Bz
7 : R=*p*-Br-Bz
8 : R=(-)-MTPA
9 : R=(+)-MTPA

Figure 1.



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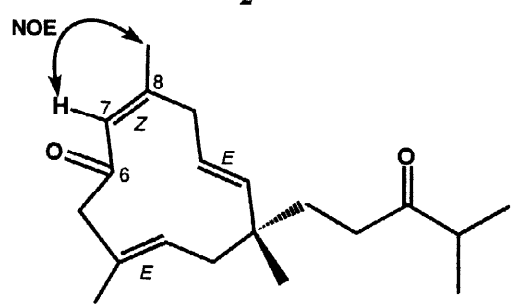

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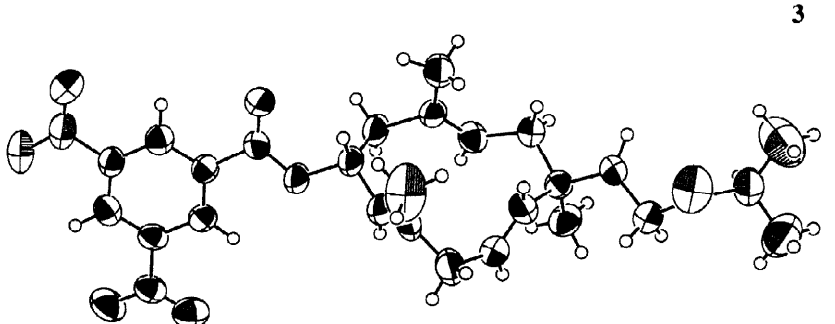


Figure 2. ORTEP Drawing of **6**

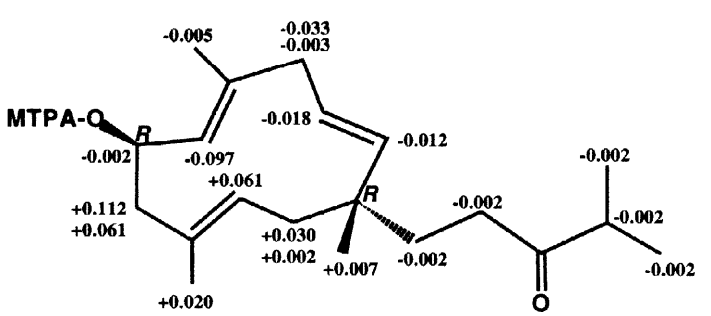
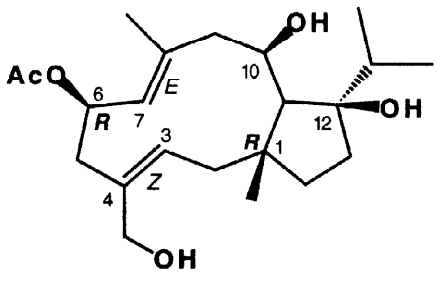


Figure 3. △δ values [$\delta_{(-)}$ - $\delta_{(+)}$] for the MTPA esters (**8** and **9**)

Denudatenone C (**3**) has the same molecular formula ($C_{20}H_{32}O_2$) as that of denudatenone B (**2**). The spectral data (IR, UV, ^1H and ^{13}C NMR) of **3** were quite similar to those of **2** except for the observation of an olefinic proton [δ 5.87 (1H, s)] in high field at H-6 compared with an olefinic proton [δ 6.53 (1H, s)] at H-6

of **2**. The relative structure of **3** was deduced from careful analysis of the 2D NMR spectra including DQF-COSY, HMQC, HMBC and NOESY (NOE between H-6 and H-19) to be the 6, 7-*Z* form of **2**.

The IR spectrum of acetoxyodontoschismenetriol (**4**) ($C_{22}H_{36}O_5$) indicated the presence of a hydroxyl group (3250 cm^{-1}) and an acetoxyl (1735 cm^{-1}) group. The ^1H and ^{13}C NMR spectra of **4** showed the presence of a primary [δ_H 3.89, 4.19 (each *d*, *J*=12.4 Hz)], a secondary [δ_H 4.09 (*dd*, *J*=4.1, 11.5 Hz)], and a tertiary [δ_C (90.2, s)] alcohol, and an acetoxyl [δ_H 2.05 (3H, *s*)] group. The relative structure of **4** was deduced from careful analysis of HMBC and NOESY spectra, and finally established by X-ray crystallography[10] as shown in Figure 4. The absolute configuration of **4** was elucidated by two experimental results described below. The three-step reactions [i) 2,2-dimethoxypropane/*p*-TsOH; ii) *t*-Bu(Me)$_2$SiCl/Et$_3$N/DMAP; iii) LiAlH$_4$] of **6** afforded compound **10.** A *p*-bromobenzoate **11** of **10** showed a negative Cotton effect at 241nm ($\Delta\varepsilon$ -10.5) in the CD spectrum. Compound **10** was esterified with (-)- and (+)-MTPA, DCC and DMAP in CH_2Cl_2 to afford the (-)-MTPA ester (**12**) and the (+)-MTPA ester (**13**), respectively. The $\Delta\delta$ values [$\delta_{(-)}$-$\delta_{(+)}$] are shown in Figure 5, indicating that the absolute configuration of C-6 of **4** was represented as *R*. The absolute configuration of acetoxy-odontoschismenetriol (**4**) was thus determined as (1*R*, 6*R*, 10*R*, 11*S*, 12*R*)-6-acetoxy-10, 12, 16-trihydroxydolaballa-3*Z*, 7*E*-diene.



4

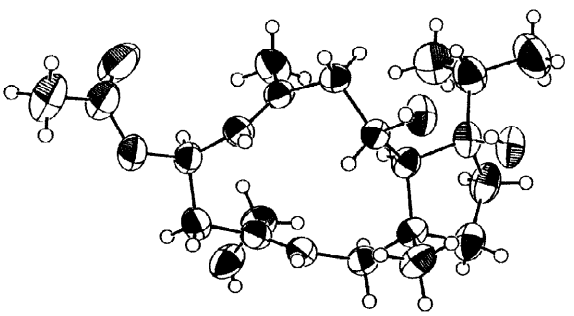
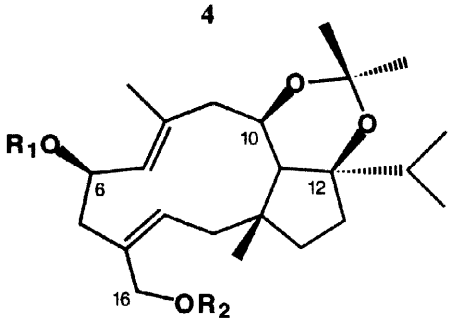


Figure 4. ORTEP Drawing of **4**



10 : R_1= H ; R_2= Si-*t*-Bu(Me)$_2$

11 : R_1= *p*-Br-Bz ; R_2= Si-*t*-Bu(Me)$_2$

12 : R_1= (-)-MTPA ; R_2= Si-*t*-Bu(Me)$_2$

13 : R_1= (+)-MTPA ; R_2= Si-*t*-Bu(Me)$_2$

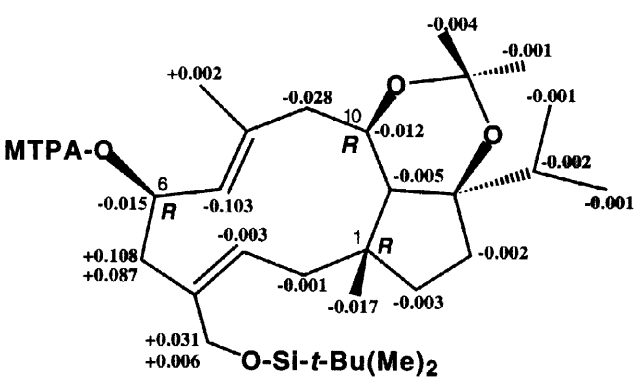
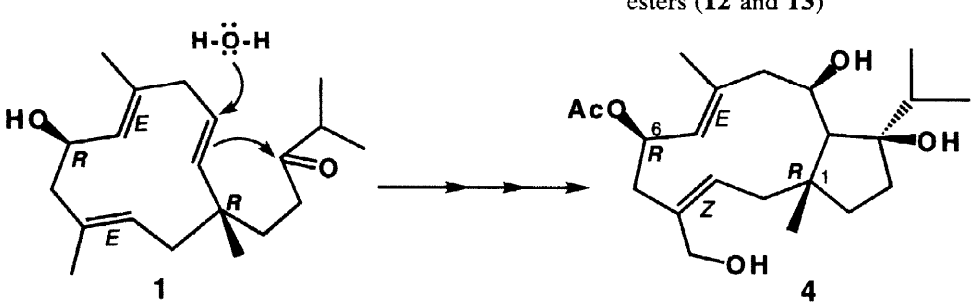


Figure 5. $\Delta\delta$ Values [$\delta_{(-)}$ - $\delta_{(+)}$] for the MTPA esters (**12** and **13**)



1 **4**

Figure 6. Possible Biogenetic Pathway of **4**

Vibsane-type diterpenoids isolated from *Viburnum awabuki* belonging to Caprifoliaceae are very rare compounds in nature.[11] *Ent*-vibsane-type diterpenoids, denudatenones from the liverwort *O. denudatum*, were the first reported example in nature. Dolabellane-type diterpenoid **4** might be biosynthesized through denudatenone A (**1**) by a series of cyclizations as shown in Figure 6.

References and Notes

1. Y. Asakawa, "Chemical Constituents of Hepaticae," in "*Progress in the Chemistry of Organic Natural Products*" (W. Herz, H.Grisebach, and W. G. Kirby eds.),Vol. **42**, p. 1. Wien -New York, Springer (1982).
2. Y. Asakawa, Chemical Constituents of Bryophytes in "*Progress in the Chemistry of Organic Natural Products*" (W. Herz, W. G. Kirby, Moore, W.Steglich and Ch. Tamm eds.), Vol. **65**, P. 1. Wien-NewYork, Springer (1996).
3. A. Matsuo, K. Kamio, K. Uohama, K. Yoshida, J. D. Conolly, and G. A. Sim, *Phytochemistry*, **27**, 1153 (1988).
4. **1** : colorless oil; $[\alpha]_D^{24}$ +222.0° (*c* 0.41, $CHCl_3$); HR-MS: *m/z* 304.2387, $C_{20}H_{32}O_2$ requires 304.2402; EI-MS: *m/z* 304 (M^+), 286, 235 (100), 147, 132; 71; FT-IR (KBr) cm^{-1}: 3402 (OH), 1711 (C=O), 1013; ^1H NMR($CDCl_3$): δ 1.04 (3H, *s*, 20-H), 1.07, 1.08 (each 3H, *d*, *J*=7.1 Hz, H-16, H-17), 1.43 (3H, *br.s*, H-18), 1.75 (3H, *br.s*, H-19), 4.53 (1 H, *ddd*, *J*=5.5, 9.9, 9.9 Hz, H-5), .4.99 (1H, *br. d*, *J*=9.9 Hz, H-6), 5.03 (1H, *dd*, *J*=3.6, 9.6, H-2), 5.04 (1H, *dd*, *J*= 1.1, 16.2 Hz, H-10), 5.63 (1H, *ddd*, *J*=6.9, 7.7, 16.2 Hz, H-9); ^{13}C NMR ($CDCl_3$): δ 66.3 (*d*, C-5), 125.7 (*d*, C-2), 129.7 (*d*, C-9), 130.7 (*d*, C-6), 132.2 (*s*, C-3), 139.5 (*d*, C-10), 142.4 (*d*, C-7), 215.2 (*s*, C-14).
5. **2** : colorless oil; $[\alpha]_D^{24}$ +375.5° (*c* 0.87, $CHCl_3$); HR-MS: *m/z* 302.2224, $C_{20}H_{30}O_2$ requires 302.2246; EI-MS: *m/z* 302 (M^+), 234, 149 (100), 96; FT-IR (KBr) cm^{-1}: 1711, 1692 (C=O), 1632, 1194, 1113, UV (EtOH)λ_{max} nm (log ε): 203 (4.02), 243 (3.72); ^1H NMR($CDCl_3$): δ 1.09, 1.10 (each 3H, *d*, *J*=6.9 Hz, H-16, H-17), 1.13 (3H, *s*, H-20), 1.45 (3H, *br.s*, H-18), 2.00 (3H, *br.s*, H-19), 2.81, 3.04 (each 1H, *d*, *J*=13.5 Hz, H-4), 5.18 (1H, *d*, *J*=16.2, H-10), 5.42 (1 H, *dd*, *J*=4.9, 10.7 Hz, H-2), 5.59 (1H, *ddd*, *J*=7.3, 7.3, 16.2 Hz, H-9), 6.53 (*s*, H-6); ^{13}C NMR ($CDCl_3$): δ 126.9 (*d*, C-9), 127.9 (*d*, C-6), 128.3 (*d*, C-2), 132.7 (*s*, C-3), 143.4 (*d*, C-10), 155.3 (*s*, C-7), 200.3 (*s*, C-5), 214.9 (*s*, C-14).
6. **3** : colorless oil; $[\alpha]_D^{24}$ +64.3°(*c* 0.76, $CHCl_3$); HR-MS: *m/z* 302.2229, $C_{20}H_{30}O_2$ requires 302.2246; EI-MS: *m/z* 302 (M^+), 234, 216, 149, 96 (100%); FT-IR (KBr) cm^{-1}: 1711, 1684 (C=O), 1632 (C=C), 1109; UV (EtOH) λ_{max}nm (log ε): 230 (3.73); ^1H NMR($CDCl_3$): δ0.99 (3H, *s*, H-20),1.07, 1.08 (each 3H, *d*, *J*=6.9 Hz, H-16, H-17), 1.72 (3H, *br.s*, H-18), 1.89 (3H, *br.s*, H-19), 2.86, 3.01 (each 1H, *d*, *J*=11.3 Hz, H-4), 4.93 (1H, *dd*, *J*=1.1, 15.9 Hz, H-10), 5.18 (1H, *dd*, *J*=4.7, 10.2 Hz, H-2), 5.25 (1H, *ddd*, *J*=7.3, 7.3, 15.9 Hz, H-9), 5.87 (*s*, H-6); ^{13}C NMR ($CDCl_3$): δ 125.6 (*d*, C-9), 126.3 (*d*, C-6), 128.0 (*d*, C-2), 128.2 (*s*, C-3), 137.7 (*d*, C-10), 150.1 (*s*, C-7), 200.6 (*s*, C-5), 215.0 (*s*, C-14).
7. **4** : colorless prism, mp 208-210°, $[\alpha]_D^{25}$ +33.3° (*c* 0.60, EtOH); EI-MS: *m/z* 362 (M^+-H_2O), 302, 151 (100), 123; CI-MS (CH_4): *m/z* 379 (M^+-1), 285 (100); FT-IR (KBr)cm^{-1}: 3231 (OH), 1743 (C=O), 1236, 1055; ^1H NMR ($CDCl_3$): δ0.94, 0.97 (each 3H, *d*, *J*=6.9 Hz, H-19, H-20), 1.34 (3H, *s*, H-15), 1.77 (3H, *br.s*, H-17), 2.05 (3H, *s*, -OAc), 3.89, 4.19 (each 1H, *d*, *J*=12.4 Hz, H-16), 4.09 (1H, *dd*, *J*= 4.1, 11.5 Hz, H-10), 5.12 (1H, *dt*, *J*=1.3, 10.7 Hz, H-7), 5.32 (1H, *dd*, *J*=2.7, 12.9 Hz, H-3), 5.62 (1H, *ddd*, *J*=5.2, 10.7, 10.7 Hz, H-6), ^{13}C NMR ($CDCl_3$): δ59.4 (*t*, C-16), 70.5 (*d*, C-6), 76.3 (*d*, C-10), 90.2 (*s*, C-12), 126.5 (*d*, C-7), 130.5 (*d*, C-3), 135.6 (*s*, C-4), 136.7 (*s*, C-8), 171.1 (*s*, OAc).
8. The crystal data for **6** are as follows : monoclinic; space group $P2_1$ with *a*=21.997 (2), *b*=6.108 (2), *c*=20.162 (3)Å, V=2683.2 (9)Å^3, β=97.90 (1)°, Z=4, and μ(Cu K-α)=6.973cm^{-1} by Mac Science MXC 18 instrument. Final R value was 0.057 for 3385 reflections. The supplementary materials have been deposited at the Cambridge Crystallographic Data Center.
9. T. Kusumi, T. Hamada, M. O. Ishitsuka, I. Ohtani and H. Kakizawa, *J. Org. Chem.*, **57**, 1033 (1992).
10. The crystal data for **4** are as follows : monoclinic; space group $P2_12_12_1$ with *a*=114.82 (6), *b*=20.82 (7), *c*=14.121 (5)Å, V=4357.1 (3)Å^3, Z=82, and μ(Cu K-α) =6.132cm^{-1} . Final R value was 0.056 for 2770 reflections.
11. Y. Fukuyama, H. Minami, K. Takeuchi, M. Kodama, and K. Kawazu, *Tetrahedron Lett.*, **37**, 6767.