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REPRINTED FROM

CHEMISTRY LETTERS

The Chemical Society of Japan

1984

CHEMISTRY LETTERS, pp. 599 - 602, 1984.

(+)-ACETOXYODONTOSCHISMENOL, A NEW DOLABELLANE DITERPENOID FROM THE LIVERWORT *ODONTOSCHISMA DENUDATUM*

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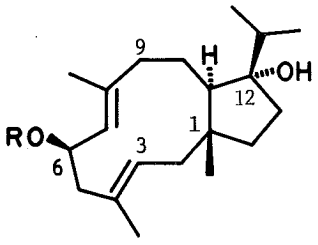
A new dolabellane diterpenoid, (+)-acetoxyodontoschismenol, displaying antifungal properties, has been isolated from the liverwort *Odontoschisma denudatum*, and its structure, including the absolute configuration, has been determined as (1R,6R,11R,12S)-6-acetoxy-12-hydroxydolabella-3*E*,7*E*-diene on the basis of the chemical and spectroscopic evidence.

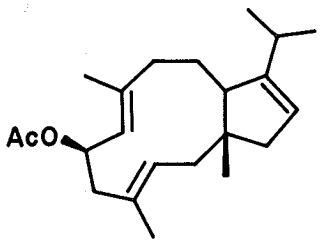
Liverworts (Hepaticae) form a special group considered to be an early stage in the evolution of terrestrial plants, and generally elaborate sesquiterpenoids which are the antipodes of those found in higher plants.[1] Liverworts also produce diterpenoids though these are less common than sesquiterpenoids.[2] We have recently reported the isolation and structure determination of several diterpenoids based on the verrucosane and neoverrucosane carbon skeletons.[3]

In continuing our investigation on the diterpenoid constituents of liverworts we have isolated a new diterpenoid, (+)-acetoxyodontoschismenol (1), with antifungal activity, from the liverwort *Odontoschisma denudatum* (Nees) Dum. which grows on decayed wood. On the basis of the following chemical and spectroscopic evidence, the structure and absolute configuration of this dolabellane diterpenoid has been established as (1R,6R,11R,12S)-6-acetoxy-12-hydroxydolabella-3*E*,7*E*-diene (1).

(+)-Acetoxyodontoschismenol (1), $C_{22}H_{36}O_3$, mp 75-76 °C; $[\alpha]_D$ +66.2° (c 0.9, $CHCl_3$), was isolated as a major component of the ethyl acetate extract of the plant in 6.3% yield.[4] The spectroscopic properties suggested that this compound (1) was a bicyclic diterpenoid containing a secondary acetoxy group [IR ($CHCl_3$) 1730, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (3H, s), 5.63 (1H, ddd, J=11.0, 11.0, and 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 69.5 (d)], a tertiary hydroxy [IR 3635, 3510 cm^{-1}; δ_C 87.3 (s)], and two trisubstituted double bonds with a methyl group [IR 1680, 850 cm^{-1}; δ_H 1.59 (3H, t, J=1.0 Hz), 1.79 (3H, d, J=1.0 Hz), 5.10 (1H, br.d, J=11.0 Hz), 5.20 (1H, br.d, J=13.0 Hz); δ_C 139.9 (s), 131.9 (s), 127.4 (d), 125.4 (d)]



1 R=Ac
2 R=H
8 R=*p*-BrC_6H_4CO



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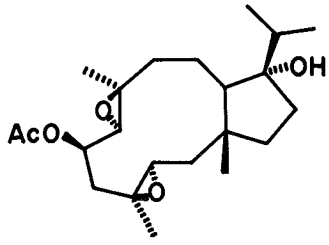

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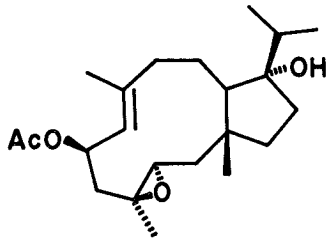

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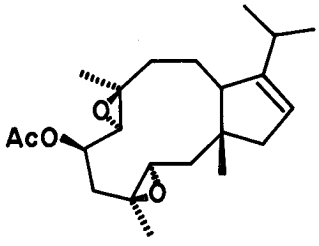

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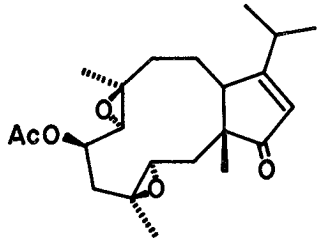

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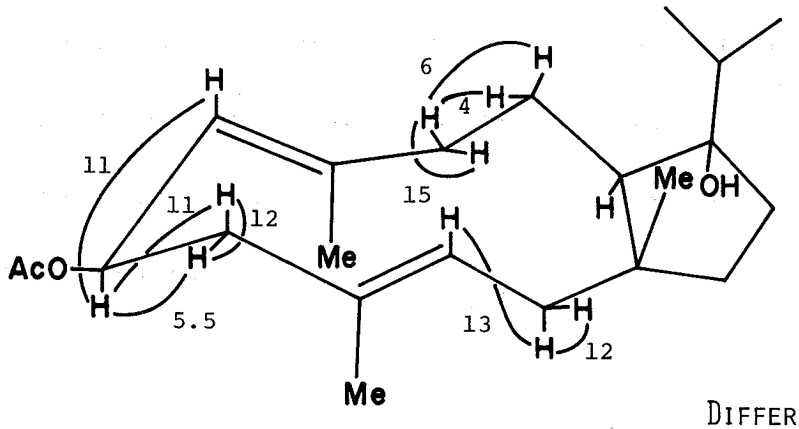
as well as an isopropyl group [IR 1390, 1380 cm^{-1}; δ_H 0.93 and 0.99 (each 3H, d, J=7.0 Hz); δ_C 46.2 (d) or 35.0 (d)] and a tertiary methyl [δ_H 1.06 (3H, s); δ_C 44.4 (s)].[5] Other features of the ^{13}C NMR spectrum included six methylene carbons [δ 45.5, 43.4, 40.8, 36.0, 30.4, and 25.9 (each t)] and one methine carbon [δ 35.0 (d) or 46.2 (d)]. The acetoxy-alcohol (1) was converted into the diol (2), $C_{20}H_{34}O_2$, mp 139-140 °C; $[\alpha]_D$ +57.9° (c 1.5, $CHCl_3$) [IR 3620, 3450, 1670, 885 cm^{-1}; ^1H NMR δ 4.62 (1H, ddd, J=10.0, 10.0, and 5.0 Hz)] by alkaline hydrolysis. Dehydration of 1 with $SOCl_2$ in pyridine afforded the triene (3), $C_{22}H_{34}O_2$ [IR 1725, 1665, 860 cm^{-1}; ^1H NMR δ 5.23 (1H, br.s, w/2=6.0 Hz)]. Under reflux with two equivalents of MCPBA in $CHCl_3$ both trisubstituted double bonds of 1 were oxidized to give the diepoxide (4), $C_{22}H_{36}O_5$, mp 109-110 °C; $[\alpha]_D$ +31.9° (c 1.3, $CHCl_3$) [^1H NMR δ 2.89 (1H, d, J=9.0 Hz), 3.08 (1H, dd, J=8.0 and 2.0 Hz)].[6] However, on oxidation of 1 with one equivalent MCPBA in CH_2Cl_2 at room temperature only one of the double bonds was oxidized yielding the monoepoxide (5), $C_{22}H_{36}O_4$, mp 104-105 °C; $[\alpha]_D$ +63.5° (c 1.2, $CHCl_3$) [^1H NMR δ 2.88 (1H, dd, J=10.0 and 2.0 Hz), 5.21 (1H, br.d, J=10.0 Hz)].

In order to establish the size of the ring bearing the tertiary hydroxy group, the diepoxide (4) was first treated with $POCl_3$ in pyridine to afford the dehydration product (6), $C_{22}H_{34}O_4$, mp 132-133 °C; $[\alpha]_D$ +35.9° (c 0.9, $CHCl_3$) [^1H NMR δ 5.28 (1H, br.s, w/2=4.0 Hz)]. This was submitted to allylic oxidation with Collins reagent to give the enone (7), $C_{22}H_{32}O_5$, $[\alpha]_{D_1}$ -53.3° (c 0.2, $CHCl_3$) [UV (C_2H_5OH) 230 nm (ε 12000); IR 1740, 1706, 1620 cm^{-1}; ^1H NMR δ 5.90 (1H, br.s,

w/2=2.0 Hz)] whose ^{1}H NMR spectrum had no proton signals adjacent to the carbonyl group, except for the vinyl proton. The IR carbonyl band at 1706 cm^{-1} indicated the presence of an α,β-unsaturated cyclopentenone in the molecule (7).

From the above chemical and spectroscopic evidence and by application of the biogenetic isoprene rule[7] the carbon framework of the original compound (1) was deduced to be the known dolabellane skeleton.[8] The relative configuration of the C(12)-tertiary hydroxy group in this dolabellane skeleton is *trans* to the C(1)-methyl group and *cis* to the C(11)-methine hydrogen atom since the tertiary methyl showed only a very small pyridine-induced solvent shift [^{1}H NMR δ 1.06 in $CDCl_3$ and δ 1.18 in C_5D_5N][9] and also suffered only a weak lanthanide-induced shift [Δ Eu 2.68] on addition of the shift reagent Eu(dpm)$_3$.[10] In addition, the dehydration reaction did not produce any products with a C(11)-C(12) double bond, the C(12)-C(13) double bond being the major product. The 360 MHz ^{1}H NMR spectrum of the acetoxy-alcohol (1) had proton signals for the 5β-H, 2α-H, 9β-H, and 5α-H at δ 2.10 (1H, dd, J=12.0 and 11.0 Hz), 2.16 (1H, dd, J=13.0 and 12.0 Hz), 2.31 (1H, ddd, J=15.0, 6.0, and 4.0 Hz), and 2.50 (1H, dd, J=12.0 and 5.5 Hz), respectively, in addition to those of 3-H, 4-Me, 6α-H, 7-H, and 8-Me described above. The assignments of these proton signals were established by coupling pattern analysis, and the coupling constants, obtained by extensive decoupling experiments, supported the stereostructure shown in the following drawing. Geometries of the C(3)-C(4) and C(7)-C(8) double bonds were certified to be *trans* or *E* on the basis of NOE experiments, exhibiting no effects between the vinyl methyls and the vinyl protons. Furthermore, difference NOE experiments revealed the relative configuration and the conformation of the cycloundeca-1,5-diene ring. Finally, the absolute configuration was elucidated by the exciton chirality method of the CD spectrum [$\lambda_{ext.}$ (C_7H_{16}) 240 nm (Δε -8.36)] of the allylic *p*-bromobenzoate (8), $C_{27}H_{37}O_3Br$, mp 67-68 °C [UV (C_2H_5OH) 244 nm (ε 9760); IR 1706, 1264 cm^{-1}].[11]



DIFFERENCE NOE

Me irradiated	H enhanced
1-Me	3-H (13%)
4-Me	6α-H (10%)
8-Me	6α-H (10%)

Thus, the structure including the absolute configuration of the new diterpenoid, (+)-acetoxyodontoschismenol, has been determined to be (1R,6R,11R,12S)-6-acetoxy-12-hydroxydolabella-3*E*,7*E*-diene (1). The natural acetoxy-alcohol (1) and its reaction products, (2, 4, and 5), inhibited the growth of some pathogenic fungi which cause plant diseases.

We thank Dr. K. Kuriyama, Shionogi Research Institute, for determination of the CD spectrum and Dr. I. Sadler, University of Edinburgh, for the 360 MHz ^{1}H NMR spectrum. Part of this work was supported by a Grant-in-Aid (58540335) for Scientific Research from the Ministry of Education, Science and Culture.

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4) All new compounds gave satisfactory combustion and/or mass spectrometric analysis and spectroscopic data consistent with the assigned structures.
5) ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ solution, and IR spectra in $CHCl_3$ solution.
6) Formation of the epoxy rings of the diepoxide (4) and the monoepoxide (5) should have performed through peripheral attack of the peracid to the double bonds.
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(Received January 23, 1984)