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NEW HIGHLY OXIDIZED FUSICOCCANE DITERPENOIDS FROM THE LIVERWORT *Plagiochila acanthophylla* subsp. *japonica*

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Abstract: Four novel fusicoccane diterpenoids, fusicoplagins A, B, C, and D, have been isolated from the liverwort *Plagiochila acanthophylla* subsp. *japonica* and the structures determined by spectroscopic methods, chemical transformations, and X-ray crystallographic analysis.

The *Plagiochila* species (liverworts)[1], *P. fruticosa*, *P. hattoriana*, *P. ovalifolia*, and *P. yokogurensis*, produce *ent*-2,3-seco-aromadendrane-type sesquiterpene hemiacetals, one of which, plagiochiline A,[1] possesses a characteristic pungency and exhibits very strong antifeedant activity against the African army worm, *Spodoptera exempta* at 1-10 ng/cm^2.[1] However, no plagiochiline A has been detected[1] in *P. acanthophylla* subsp. *japonica* and instead bicyclohumulenone[2], *ent*-maalioxide[3], and *ent*-cyclocolorenone[3] have been isolated. As a continuation of our work on the bioactive constituents of the Hepaticae, reexamination of *P. acanthophylla* subsp. *japonica* has been carried out. Herein we report the isolation and structure determination of four new highly oxidized fusicoccane diterpenoids, fusicoplagins A, B, C, and D, by spectroscopic methods, chemical transformations, and X-ray crystallographic analysis.

The ethyl acetate soluble portion of a methanol extract of fresh *P. acanthophylla* subsp. *japonica* was subjected to column chromatography over silica gel to afford four new diterpenes, fusicoplagins A, B, C, and D, together with the previously known sesquiterpenes, β-barbatene,[1] bicyclohumulenone,[2] *ent*-maalioxide,[3] and *ent*-cyclocolorenone.[3]

Fusicoplagin A (1) showed the molecular formula, $C_{24}H_{38}O_7$ ($(M+1)^+$ m/z 439.2690), by chemical ionization-high resolution mass spectrometry (CI-HRMS). The IR spectrum of 1 indicated the presence of hydroxyl (3575 and 3530 cm^{-1}) and carbonyl (1735 and 1715 cm^{-1}) groups. The COSYP spectrum[4] of 1, shown in Fig. 1, and NOESY as well as NOE difference spectra suggested the presence of the partial structures A-D. The ^{13}C NMR spectrum showed five methyls (δ_C 16.9,

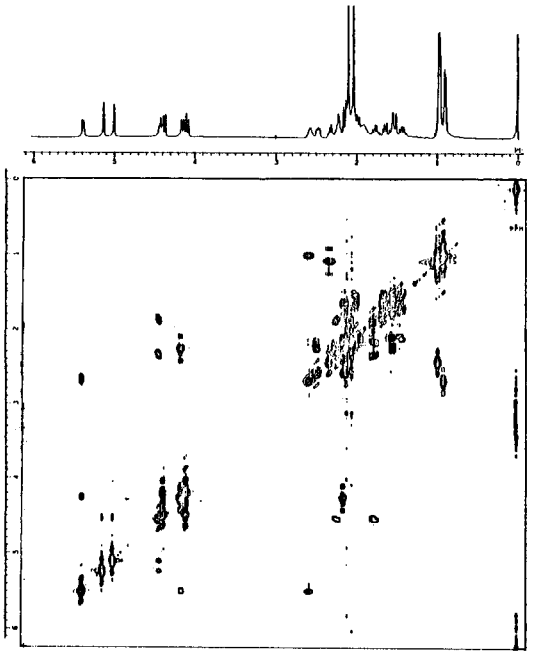
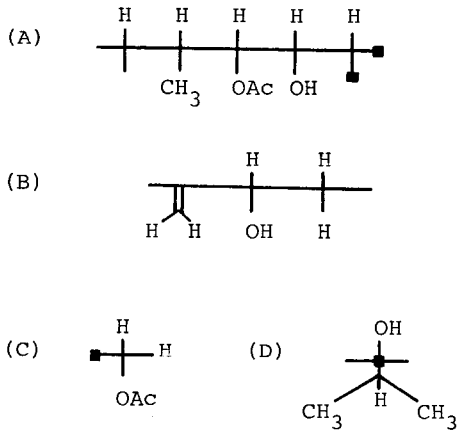
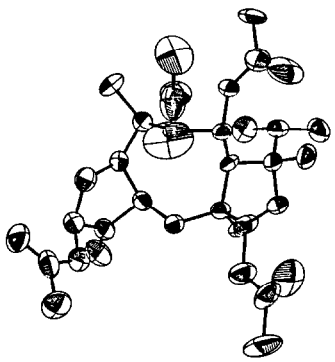


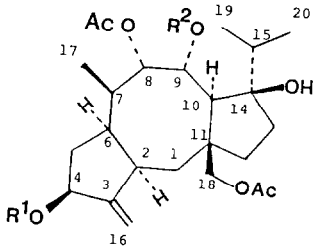
Fig. 1. COSYP spectrum of 1 (400 M Hz).

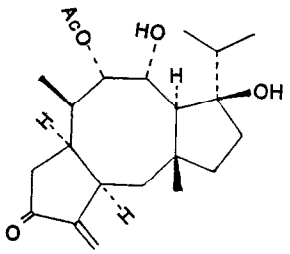


[■ denotes a quaternary carbon]



Perspective drawing of 6.





4

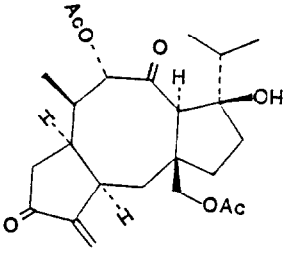
1 $R^1=R^2=H$

2 $R^1=H$, $R^2=Ac$

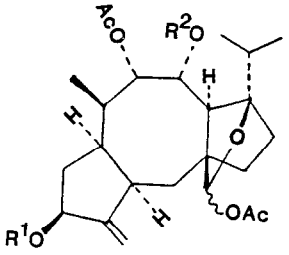
5 $R^1=Ac$, $R^2=H$

6 $R^1=R^2=Ac$

8 $R^1=p\text{-}BrBz$, $R^2=H$



7



3 $R^1=R^2=H$

9 $R^1=Ac$, $R^2=H$

10 $R^1=R^2=Ac$

17.3, 18.6, 20.9, and 21.0), five methylenes (δ_C 30.8, 33.2, 34.8, 38.8, and 68.2), eight methines (δ_C 31.8, 38.0, 42.6, 44.1, 47.6, 71.2, 72.0, and 72.5), and two quaternary carbons (δ_C 45.8 and 85.7) as well as two olefins (δ_C 108.6 (t) and 161.2 (s)) and two carbonyls (δ_C 169.9 (s) and 171.2 (s)). Acetylation (Ac_2O/Py) of 1 gave the triacetate 5, whilst the tetraacetate 6 (mp 223.5-225) was obtained on acetylation (Ac_2O/Py) with 4-dimethylaminopyridine (DMAP). The partial structure B was confirmed by UV absorption (λ_{max} 234 nm log ε=3.88) of the diketone 7 obtained by Jones oxidation of 1. From these observations, 1 was inferred to have a fusicoccane skeleton and was formulated as shown. However, as it was difficult to establish the stereostructure by spectroscopic methods, single crystal X-ray analysis of the tetraacetate 6 was undertaken. The crystals of 6 belong to orthorhombic, space group $P2_12_12_1$, and the lattice parameters are a=17.758(5), b=16.609(2), and c=10.343(3) Å. The diffraction intensities were collected in the ω scan by using graphite-monochromated Mo-K_α radiation. The structure was solved by direct methods and the final R value was 0.077 for 1674 reflections. The absolute stereochemistry of the 4-position of the p-bromobenzoate 8 was determined to be S by the allylic benzoate chirality method[5], since the CD spectrum of 8 showed a positive Cotton effect at 244.0 nm (Δε +7.51). The absolute stereochemistry of 1 was thus established as shown.

The spectral data (Table 1) of fusicoplagin B (2), $C_{26}H_{40}O_8$ (CI-HRMS), were quite similar to those of 1. The proton observed at δ 4.15 (dd, J=11.2 and 2.2 Hz) due to H-9 of 1 shifted downfield to δ 5.50 (dd, J=11.2 and 2.2 Hz), suggesting that 2 was the 9-O-acetate of 1. Acetylation (Ac_2O/Py) of 2

Table 1. ^1H NMR data of 1 - 10 (400 MHz in $CDCl_3$ at 24°C, * 4 and 7 measured in Py-d_5 at 90°C).

position	1	2	3	4*	5	6	7*	8	9	10
4	4.42 t (7.6)	4.50 t (7.6)	4.50 t (7.6)	----	5.43 t (7.6)	5.44 t (7.6)	----	5.68 t (7.6)	5.44 t (7.6)	5.49 t (7.6)
8	5.37 dd (7.3,2.2)	5.43 dd (7.8,2.2)	5.55 dd (7.3,2.2)	5.61 dd (8.8,2.2)	5.38 dd (7.3,2.2)	5.38 dd (7.3,2.2)	5.77 d (8.5)	5.43 dd (7.3,2.2)	5.55 dd (7.3,2.2)	5.54 dd (7.1,2.7)
9	4.15 dd (11.2,2.2)	5.50 dd (11.2,2.2)	4.05 dd (8.3,2.2)	4.76 dd (10.3,2.2)	4.15 dd (11.2,2.2)	5.50 dd (11.2,2.2)	----	4.18 dd (11.2,2.2)	4.05 dd (8.3,2.2)	5.48 dd (8.8,2.7)
15	2.32 sept (6.6)	2.35 sept (6.6)	2.30 m	2.78 sept (6.8)	2.32 sept (6.8)	2.40 m	2.76 m	2.32 sept (6.8)	2.24 m	2.30 m
16	4.99 s 5.12 s	4.95 s 5.11 s	4.95 s 5.11 s	5.20 d 6.10 d (2.7)	5.04 s 5.09 s	5.00 s 5.06 s	5.25 d 6.06 d (2.2)	5.08 s 5.18 s	4.98 s 5.04 s	4.99 s 5.06 s
17	0.89 d (7.3)	0.90 d (7.2)	0.88 d (7.3)	0.91 d (7.1)	0.89 d (7.3)	0.90 d (7.1)	0.94 d (6.8)	0.92 d (7.3)	0.88 d (7.3)	0.89 d (6.8)
18	4.08 d 4.37 d (11.2)	4.36 d 4.53 d (11.5)	5.74 s	1.52 s	4.09 d 4.38 d (11.2)	4.37 d 4.49 d (11.2)	4.54 d 4.81 d (11.2)	4.15 d 4.41 d (11.2)	5.74 s	5.75 s
19, 20	0.95 d 0.97 d (6.6)	0.92 d 0.94 d (6.6)	0.99 d 1.04 d (6.8)	1.12 d 1.16 d (6.8)	0.96 d 0.98 d (6.8)	0.93 d 0.94 d (7.1)	0.97 d 1.01 d (7.1)	0.98 d (6.8)	0.99 d 1.04 d (6.8)	0.90 d 0.95 d (6.6)
Ac	2.03 s 2.10 s	2.00 s 2.05 s 2.09 s	2.09 s 2.12 s	1.88 s	2.04 s 2.07 s 2.10 s	2.00 s 2.05 s 2.09 s x2	1.97 s 2.11 s	2.01 s 2.09 s	2.08 s 2.09 s 2.12 s	1.97 s 2.07 s 2.10 s 2.20 s

[s=singlet, d=doublet, m=multiplet, dd=double doublet, sept=septet]

gave the tetraacetate 6 and hence 2 was determined to have the structure shown.

Fusicoplagin C (3) showed an acetal proton at δ 5.72 (s) whilst the AB system due to 2H-18 observed in 1 was absent from the ^{1}H NMR spectrum of 3. Acetylation (Ac_2O/Py) gave 9 and 10 (with DMAP). The structure of 3 was determined by comparing its spectral data with those of 9 and 10 and by the chemical transformation [1) $LiAlH_4$ 2) Ac_2O/Py/DMAP] of 9 into 6.

Fusicoplagin D (4), $C_{22}H_{34}O_5$ (CI-HRMS), exhibited IR absorptions due to hydroxyl (3420 and 3475 cm^{-1}) and carbonyl (1740 and 1715 cm^{-1}) groups and UV absorption at 234.5 nm (log ε=3.73). Both the ^{1}H and ^{13}C NMR spectra of 4 in $CDCl_3$ at rt showed only broad peaks presumably as a result of restricted rotation. However, sharp spectra were obtained in Py-d_5 at 90°C. The presence of one tertiary and three secondary methyl groups along with the absence of signals characteristic of a hydroxymethyl group indicated that C-18 was unsubstituted. By comparing the spectral data with those of 1-3, the structure of 4 was determined as shown.

Fusicoccanes are relatively rare in Nature but have been found in fungi,[6,7] liverworts,[8] and higher plants.[9] They presumably arise by a similar biosynthetic pathway to those which afford the dolabellanes[10] and the verrucosanes,[11] both of which are present in liverworts.

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