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NEW OXIDISED *ENT*-ATISENE DITERPENES FROM *EUPHORBIA FIDJIANA*

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Abstract. The heartwood of *Euphorbia fidjiana* Boiss. has yielded three oxygenated *ent*-atisene diterpenoids, *ent*-13[R]-hydroxy-3,14-dioxo-16-atisene **[1]**, *ent*-3,14-dioxo-16-atisene **[2]** and *ent*-13[R],14[R]-dihydroxy-3-oxo-15-atisen-17-al **[3]**. The structure and relative stereochemistry were determined from detailed nmr studies and an X-ray structure of **[1]**. **[1]** is converted in air into **[3]**.

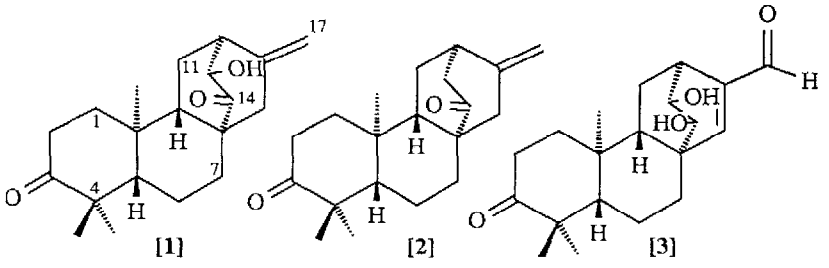
The family *Euphorbiaceae* is of considerable interest for its anti-leukaemic and co-carcinogenic compounds.[1] As part of an ongoing phytochemical study of Fijian medicinal plants,[2] we have examined extracts of the heartwood of *Euphorbia fidjiana* Boiss. Preparations from this plant are used for a variety of ailments such as constipation, weaning infants, eczema, headache, stomach-ache and tuberculosis.[3] We report here the structures of three new oxidised *ent*-atisene diterpenes isolated by multiple column chromatography of an ether extract.

Compound **[1]**, mp 175-177°, $[\alpha]_D^{25}$+44° (c, 0.03, $CHCl_3$), $C_{20}H_{28}O_3$ (HRMS: *m/z* 316.2017, required 316.2036), showed absorptions for a hydrogen-bonded secondary hydroxyl group (3460, 1064 cm^{-1}), two carbonyl groups (1690 ,1720 cm^{-1}), and a 1,1-disubstituted double bond (1620, 900 cm^{-1}) in the ir spectrum. The ^1H nmr spectrum [400 MHz] confirmed the presence of an exocyclic methylene group and showed the presence of three methyl groups and that the alcohol was adjacent to a methine group. It followed that **[1]** was tetracyclic, suggesting that it was either an atisene, kaurene, or phyllocladene derivative. Examination of the homonuclear COSY-2D and the XHCORRD spectra revealed four isolated spin systems; a four-spin system [CH_2CH_2], a five-spin system [$CHCH_2CH_2$], a five-spin system [$CHCH_2CHCH$], and another four-spin system [CH_2=CCH_2] which included allylic coupling. This evidence, and in particular the [$CHCH_2CH$] system, showed that **[1]** possessed an atisene skeleton. The positions of the functional groups were assigned from examination of ^{13}C nmr [100 MHz] spectra. Thus, two quaternary carbon signals at δ 47.3 and 47.5, assigned to C 4 and C 8 respectively from a COLOC spectrum, suggested the presence of keto groups adjacent to these positions. The *gem*-dimethyl group signals at δ 21.9 and 26.1 had chemical shifts expected for a C 3 keto compound,[4] and the [CH_2CH_2] system had chemical shifts expected for C 1 and C 2. The second keto-group could be assigned to either C 7, C 14, or C 15. Since the C 15 protons showed allylic coupling to the exocyclic methylene protons, and since the C 7 protons were present in the [$CHCH_2CH_2$] system, the second keto group was assigned to C 14 and thus the hydroxyl group to C 13, thereby completing the [$CHCH_2CHCH$] system. A NOESY-2D spectrum showed a strong NOE correlation between H 13 and H $(20)_3$ indicating a 13[R] configuration for the *ent*-atisene skeleton. The *trans*-A/B,*trans*-B/C ring junctions were confirmed by the observation of ^4J coupling (0.68 Hz) between H 20, and H 5 and H 9 in the homonuclear JRESOLVED spectrum.

The relative stereochemistry of [1] was confirmed by an X-ray analysis (figure 1). The absolute stereochemistry is assumed to be as shown by analogy with that assigned to *ent*-atisane diterpenes from *Euphorbia acaulis*.[5,6] Work is in progress to confirm this.

A less polar fraction yielded [2], mp 160-164°, $[\alpha]_D^{25}$+5.5 (c 0.02, $CHCl_3$), $C_{20}H_{28}O_2$ (*m/z* 300), the ir spectrum of which revealed two CO absorptions (1705, 1695 cm^{-1}) and an olefinic group (1620, 890 cm^{-1}), as for [1]. The ^1H and ^{13}C nmr spectra each showed close similarity with those of [1] except that H 12 now appeared as a broad quintet rather than as a quartet, indicating the presence of an additional vicinal hydrogen, and C 13 was now a methylene group rather than a CHOH group. The proposed structure [2] is consistent with the above data and was corroborated by 2-D nmr experiments.

A more polar fraction yielded a minor component [3], $C_{20}H_{28}O_4$ (HRMS: *m/z* 332.1988, required 332.1988), as an oil[7]. The ir spectrum showed the presence of hydroxyl groups (3400 cm^{-1}, br), CO absorptions (1728, 1701 cm^{-1}), and unsaturation (1614, 1600 cm^{-1}, w). Comparison of the ^1H and ^{13}C nmr spectra with those of [1] indicated that the A/B ring moiety was identical. The mass spectrum revealed an initial loss of 30 m.u.(CHOH) followed by cleavage into two fragments of m.u. 151 corresponding to the ions $C_{10}H_{15}O^+$ and $C_9H_{11}O_2^+$. This is consistent with the presence of three oxygens in the C/D ring moiety. The ^1H nmr spectrum showed the presence of an aldehydic proton (δ9.55), a deshielded olefinic proton (δ6.67) and two oxygenated methine protons (δ3.86, s, br; 3.66, m). Also, the signal due to the exocyclic methylene protons and the C 15 protons of [1] at δ2.32 were absent in the spectrum of [3]. The salient features in the ^{13}C nmr spectrum were signals of an aldehydic carbon (δ188.4), a deshielded trisubstituted olefinic carbon (δ149.9), a relatively shielded tetrasubstituted olefinic carbon (δ137.2) and two oxygenated methine carbons (δ71.9, 76.1). These observations suggested the presence of a C 15—C 16 double bond conjugated to a C 17 aldehyde, and of secondary alcohols at C 13 and C 14. The stereochemistry at C 13 was assumed to be the same as in [1], and as there was no apparent coupling between H 13 and H 14 the dihedral angle was deduced to be approximately 90°, leading to the proposed structure. Spectral examination of an initially pure sample of [1] showed that it was slowly converted in air into [3].



The correlated ^{1}H and ^{13}C nmr chemical shifts for [1], [2], and [3] are listed in Table 1.

Table 1. Correlated ^{1}H and ^{13}C NMR Data for [1], [2] and [3]

Carbon	Compound [1]		Compound [2]		Compound [3]	
	$\delta^{13}C$	$\delta^{1}H$	$\delta^{13}C$	$\delta^{1}H$	$\delta^{13}C$	$\delta^{1}H$
C1	36.7	1.39,ddd 1.87,ddd	37.2	1.37,ddd 1.84,ddd	36.7	1.45,ddd 1.86,ddd
C2	34.1	2.34,ddd 2.56,ddd	34.1	2.34,ddd 2.57,ddd	34.1	2.35,ddd 2.59,ddd
C3	216.1	----	216.5#	----	216.6	----
C4	47.3	----	47.6	----	47.4	----
C5	55.2	1.32,dd	55.3	1.29,dd	54.9	1.40,m
C6	20.0	1.50,m 1.51,m	20.0	1.52,m 1.65,m	19.6	1.50,m 1.60,m
C7	30.4	0.95,m 2.41,ddd	31.2	0.92,m 2.35,ddd	30.4	1.00,m 2.76,ddd
C8	47.5	----	47.7	----	37.4	----
C9	51.1	1.66,dd	51.8	1.65,dd	51.4	1.64
C10	37.6	----	37.6	----	37.4	----
C11	25.4	1.76,ddd 2.02,ddd	27.9	1.66,ddd 1.95,ddd	23.9	1.73,m 1.78,m
C12	44.8	2.83,ddd	38.3	2.73,dddd	41.5	2.79,m
C13	75.1	3.88,d	44.6	2.32,m	76.1*	3.66,m
C14	218.1	----	216.6#	----	71.9*	3.86,s,br
C15	43.7	2.32,t 2H	42.6	2.30,m 2.34,m	149.9	6.67,d
C16	142.3	----	147.1	----	137.2	----
C17	111.1	4.86,dt 5.02,dt	107.2	4.69,dt 4.90,dt	188.4	9.55,s,br
C18	26.2	1.09,s	26.0	1.09,s	26.1	1.12,s
C19	21.9	1.01,s	21.9	1.02,s	21.8	1.03,s
C20	13.7	0.85,s	12.8	0.88,s	13.8	0.91,s

* : may be interchanged
# : may be interchanged

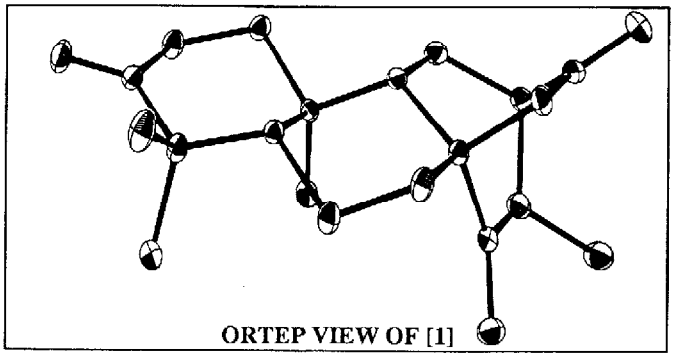


Figure 1

Compounds [1] and [2] were active against L1210 mouse leukaemia with IC_{50}>25.0.

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References

1. S.M. Kupchan, I. Uchida, A.R. Branfman, R.G. Dailey and B.Y. Fei, *Science*, **191**, 571, (1976).
2. For Part III, see R.C. Cambie, J.M. Coddington, M.J. Stone, N. Tanaka, L. Yong-hua and S. Arigayo, *Phytochem.*, in press.
3. R.C. Cambie and J. Ash, *"Fijian Medicinal Plants"*, unpublished manuscript.
4. F.W. Wehrli and T. Nishida, *Fortschr. Chem. Organ. Nat.*, **36**, 1 (1979).
5. N.K. Satti, O.P. Suri, K.L. Dhar, T. Kawasaki, K. Miyahara and N. Noda, *J. Nat. Prod.*, **50**, 790 (1987).
6. N.K. Satti, O.P. Suri, R.K. Thaper and P.L. Kachroo, *Phytochem.*, **27**, 1530 (1988).
7. UV: λ_{max} 240 nm (c 0.0015, $CHCl_3$), log ϵ 2.74.

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