4,5-Dihydroblumenol A, a New Nor-isoprenoid from Perrottetia multiflora

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4,5-DIHYDROBLUMENOL A, A NEW NOR-ISOPRENOID FROM *PERROTTETIA MULTIFLORA*

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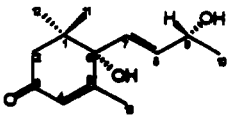
ABSTRACT.—A new carotenoid-like compound, 4,5-dihydroblumenol A [**1**], and blumenol A [**2**] were isolated from *Perrottetia multiflora* (Celastraceae). This is the first report of C-13-type metabolites from this family, and the structure of the new compound was elucidated by spectoscopic studies.

Compounds with thirteen carbon atoms, the so-called carotenoid-like (1) or nor-isoprenoids, are neither abundant nor usual as natural products. Their biogenetic origin is as yet uncertain. Some authors postulate that they may be biosynthesized from (+)-abscisic acid (2–4) by oxidative removal of the two terminal carbon atoms as in blumenol A, blumenol B and theaspirone (5,6), and others that they may be biosynthesized from carotenoids or suitable metabolites (7,8), as in the case of the damascones. They could also be produced by photooxidative processes (9) from appropriate carotenoids.

In a study of Celastraceae species used in popular medicine (10), we studied *Perrottetia multiflora* Lundell (11), and two carotenoid-like compounds [**1** and **2**] were obtained for the first time from this plant family. On investigation, these compounds proved to be, respectively, blumenol A (14–17) and a new compound, 4,5-dihydroblumenol A, the structures of which were elucidated from spectroscopic studies. The known triterpenes betulinic acid (12) and 3-*epi*-betulinic acid (13) were also isolated.

Repeated chromatography of the EtOH extract of the aerial part of *P. multiflora* on Sephadex LH-20 and Si gel yielded two compounds, **1** and **2**, with closely related spectral data. Compound **1** was identified as the previously known blumenol A (14).

The molecular formula of compound **2** was established as $C_{13}H_{22}O_3$ by high-resolution mass spectroscopy. The ^{1}H-nmr spectrum of **2** showed an ABXY$_3$ system, corresponding to the H-7, H-8, H-9 and H-10 protons, respectively, with chemical shifts and couplings similar to those of the same protons in blumenol A (see Table 1). The most notable differences in the ^{1}H-nmr spectrum were the two H-2 α-ketone protons observed in blumenol A as an AB system at δ 2.45 and 2.25 while in **2**, one proton at δ 1.92 was slightly long-range coupled with one of the H-4 protons at δ 2.25, as a consequence of the geometry H-2–C-2–C-3–C-4–H-4 in compound **2** being a chair conformation distorted by the presence



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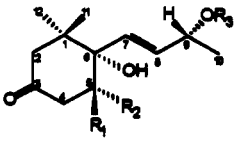

2 R_1=H, R_2=Me, R_3=H
3 R_1=Me, R_2=H, R_3=H
4 R_1=H, R_2=Me, R_3=Ac

TABLE 1. ^{1}H-Nmr (400 MHz) Data (δ, $CDCl_3$) of Compounds **1**, **2**, and **4**.[a]

Proton	Compound		
	1	**2**	**4**
2	2.45 d	2.84 d	2.83 d
	2.25 d	1.92 dd	1.91 dd
	(16.8)	(13.6,1.8)	(13.6,1.8)
4	5.91 bs	2.42 m	2.39 m
		2.23 m[b]	2.24 m[b]
5		2.27 m[b]	2.30 m[b]
7	5.79 d	5.71 d	5.75 bs[b]
	(15.7)	(15.8)	
8	5.87 dd	5.84 dd	5.75 bs[b]
	(15.7,5.1)	(15.8,5.7)	
9	4.42 m	4.44 m	5.42 m
Me-10	1.30 d	1.33 d	1.35 d
	(6.3)	(6.3)	(6.3)
Me-11	1.02 s	0.95 s	0.94 s
Me-12	1.11 s	0.97 s	0.94 s
Me-13	1.90 bs	0.88 d	0.86 d
		(6.3)	(6.3)

[a]Values based on ^{1}H-^{1}H COSY experiments, with coupling constants (J in Hz) shown in parenthesis.

[b]Overlapping signals.

of a carbonyl system in the ring. The disappearance of the β proton, at δ 5.91, of a conjugated ketone system in compound **2**, together with the transformation of a methyl singlet into a doublet compared with **1**, led us to conclude that **2** might be the 4,5-dihydro derivative of blumenol A. Signals could be seen for a carbocyclic skeleton in ^{13}C nmr (see Table 2) and the assignments were resolved by DEPT experiments, ^{1}H-^{13}C spectra (HMQC) and ^{1}H-^{13}C long-range correlation spectra with inverse detection (HMBC). The ROESY experiment contributed data to support the structure, with Figure 1 showing the preferred conformer. Data obtained from the acetyl derivative of **2**, compound **4** (Table 1), provided further information.

As the absolute stereochemistry of blumenol A is known, and compound **1** exhibited an identical [α]D to that reported in the literature (4), we assumed, on biogenetic grounds (3), that the chiral C-6 and C-9 in compound **2** would be 6*S* and 9*R*, respectively, as in blumenol A, while the new chiral center at C-5 had still to be determined. Of the various possible approaches to determine its relative configuration with regard to the other two centers, we chose to analyze the two possible epimers **2** and **3** from a theoretical reduction of the double bond C-4–C-5 in blumenol A. Study of the most stable conformations of these two epimers by molecular mechanics calculations (18), and analysis of the coupling constants of the H-5 in both epimers, showed that the theoretical values of the coupling constants of epimer **2**, but not those of epimer **3**, coincided with those of the new natural product, which were deduced, from these data, to be (5*R*)-4,5-dihydroblumenol A.

The significance of these C-13 metabolites is not fully understood, but since some carotenoids have been isolated from other Celastraceae species [β-carotene, lutein, antheraxanthin, violaxanthin and neoxanthin (19)], a carotenoid with a structure such as that found in isomytiloxanthin (20) could be the precursor of **1**

TABLE 2. ^{13}C-Nmr (100 MHz) Data (δ, $CDCl_3$) of Compounds **1** and **2**.[a]

Carbon	Compound	
	1	**2**
1	41.14	42.96
2	49.71	51.87
3	197.87	211.66
4	126.95	45.56
5	162.56	36.84
6	79.05	77.28[c]
7	135.72	132.26
8	129.00	135.58
9	68.05	58.74
10	23.76	24.33
11	22.89[b]	24.89[b]
12	24.04[b]	24.82[b]
13	18.86	16.28

[a]Values based on DEPT, HMQC, and HMBC experiments.

[b]Interchangeable values most probably as shown.

[c]Overlapping with chloroform signal.

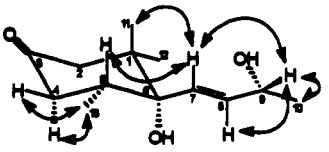

FIGURE 1. ROESY Experiment of Compound **2**.

and **2**, by degradation and/or enzymatic transformation.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Ir spectra were taken on a PE 681 spectrophotometer and ^{1}H- and ^{13}C-nmr spectra on a Bruker WP-200SY nmr spectrometer in $CDCl_3$ at 200 and 50 MHz, respectively, with TMS as internal reference. The HMBC spectrum was run on a Bruker instrument at 400 MHz. Ms were recorded on VG Micromass ZAB-2F and Hewlett-Packard 5995 mass spectrometers. Uv spectra were recorded on a Perkin-Elmer model 550-SE and optical rotations were measured on a Perkin-Elmer 241 polarimeter.

PLANT MATERIAL.—The plant, *Perrottetia multiflora* Lundell, was collected in Quebrada Bonita, Fortuna, Chiriquí, Panamá, in February 1991 and a voucher specimen (FLORPAN 688) is on file with the Unidad de Investigaciones Farmacognósticas, Facultad de Farmacia, Universidad de Panamá.

EXTRACTION AND FRACTIONATION.—The aerial part of the plant (1.048 kg) was extracted with EtOH and 9 g of the solid extract was chromatographed on Sephadex LH-20 using *n*-hexane-$CHCl_3$-MeOH (2:1:1), followed by repeated cc on Si gel to afford betulinic acid (4 mg), 3-*epi*-betulinic acid (6 mg), **1** (4 mg), and **2** (3 mg).

4,5-Dihydroblumenol A [**2**].—Compound **2** was obtained as an oil, $[\alpha]^{20}D$ +2° (*c*=0.25, $CHCl_3$); uv λ max (EtOH) 282, 212 nm; ir ν max ($CHCl_3$) 3400, 2930, 2890, 2820, 1690, 1460, 1450, 1360, 1280, 1130, 970 cm^{-1}; eims *m/z*: 226 $[M]^+$ (8), 208 ($[M-H_2O]^+$) (22), 165 (20), 141 (42), 128 (46), 109 (51), 85 (100); hrms *m/z* 226.1588 (calcd for $C_{13}H_{22}O_3$, 226.1569); ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

Acetylation of **2**.—Treatment of **2** (3 mg) with Ac_2O in pyridine (2 drops) followed by workup and purification by prep. tlc gave 9-acetoxy-4,5-dihydroblumenol A [**4**], which was obtained as an oil (2 mg) uv λ max (EtOH) 282, 220 nm; ir ν max ($CHCl_3$) 3447, 2917, 2849, 1735, 1716, 1656, 1462, 1372, 1243, 1044, 979, 758 cm^{-1}; eims *m/z* 208 $[M-Ac]^+$ (21), 152 (49), 124 (47), 123 (45), 111 (16), 110 (55), 109 (62), 95 (96), 82 (57); hrms *m/z* 208.1459 (calcd for $C_{15}H_{24}O_5$ $[M-Ac]^+$ 208.1463); ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

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