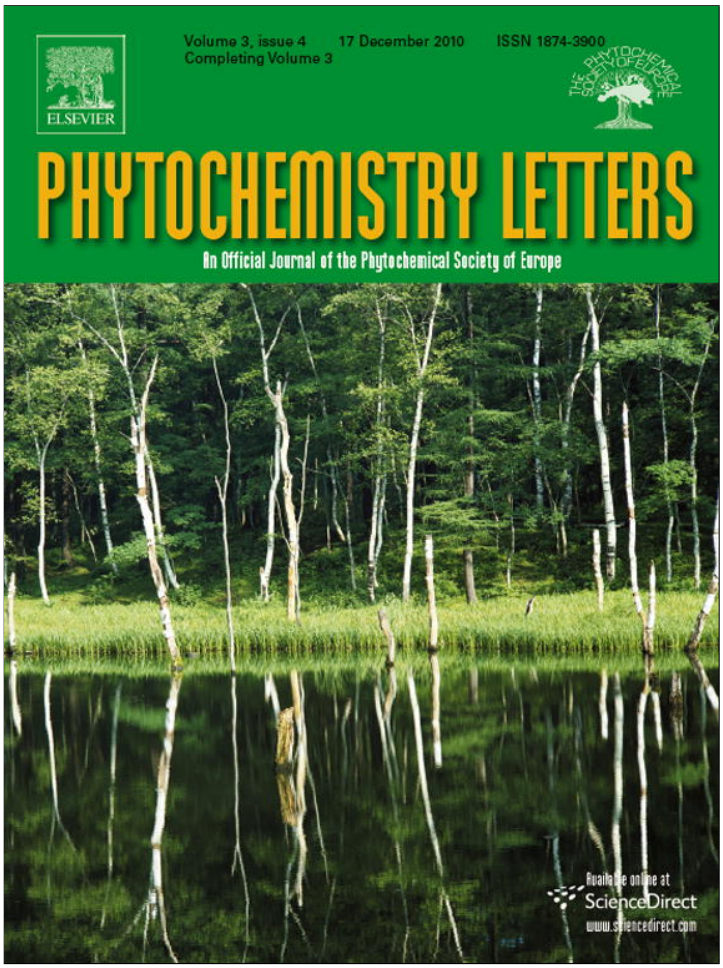

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neo-Clerodane diterpenoids from the leaf exudate of *Dodonaea angustifolia*

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ABSTRACT

Phytochemical investigation of the leaf surface exudate of *Dodonaea angustifolia* L.f. yielded two new *neo*-clerodane diterpenes, *neo*-clerodan-3,13-dien-16,15:18,19-diolide (mkapwanin) and 15-methoxy-*neo*-clerodan-3,13-dien-16,15:18,19-diolide (15-methoxymkapwanin). In addition, ten known compounds were identified. The structures were determined on the basis of spectroscopic evidence. This additional chemical information could contribute towards solving the taxonomical controversy that exists between *Dodonaea angustifolia* and *Dodonaea viscosa* Jacq., which are morphologically similar.

1. Introduction

Dodonaea angustifolia (Sapindaceae) is considered by some taxonomists to be synonymous with *Dodonaea viscosa* (Leenhouts, 1983) while others recognize it as a sub-species of *D. viscosa* (West, 1984). There are still others who recognize it as a distinct species (Beentje, 1994). *D. angustifolia* is widely distributed in four continents namely Australia, Africa, Asia and South America. In Kenya it is claimed that it exists along with *D. viscosa* (Beentje, 1994). Generation of chemical information on *D. angustifolia* and *Dodonaea viscosa* shall contribute towards understanding the relationship between these two taxa. Traditionally *D. angustifolia* is used as an analgesic, laxative, antipyretic, in rheumatism, eczema, and to treat skin ailments (Dominguez et al., 1980; Watt and Breyer-Brandwijk, 1981). The main phytochemical feature in *D. angustifolia* is the leaf surface exudate (up to 13% dry leaf weight) (Ghisalberti, 1998), which is composed of methylated flavones and flavonols in a diterpenoid (clerodane) milieu. In order to understand the taxonomic relationship between the two taxa the surface exudate of *D. angustifolia* collected from Voi (Kenya) was investigated and two new *neo*-clerodane diterpenes in addition to ten known compounds were isolated. Recently new clerodane diterpenoids and prenylated flavonoids have been reported from *D. viscosa* (Hong-Mei et al., 2010).

2. Results and discussion

HRMS of compound **1** showed a $[M+1]^+$ peak at *m*/*z* 331.1894 indicating the molecular formula $C_{20}H_{26}O_4$, and this was also evident from the ^{13}C NMR spectrum which showed resonance for twenty carbons. Compound **1** was identified as clerodane diterpene derivative by its characteristic ^1H and ^{13}C-NMR signals (Table 1), in which a tertiary methyl group appeared as a singlet at $\delta_H = 0.62$ and $\delta_C = 17.5$ assigned to CH_3-20 and a secondary methyl group as a doublet at $\delta_H = 0.86$ ($J = 6.6$ Hz) and $\delta_C = 15.5$ assigned to CH_3-17 (Ahmad et al., 2004). The presence of two α,β-unsaturated γ-lactone moieties was evident from the ^1H-NMR signals at δ 6.76 (*dd*, $J = 7.4$, 2.0 Hz) and 7.14 (*t*, $J = 1.5$ Hz) for olefinic β-protons at C-3 and C-14 respectively, the signals at δ 4.30 (*d*, $J = 8.1$ Hz), 3.92 (*dd*, $J = 8.0$, 2.0 Hz) and δ 4.79 (*d*, $J = 1.8$ Hz) were for oxymethylenes at C-19 and C-15, respectively. The corresponding carbon signals for the lactone moieties appeared at δ_C 169.3 and 174.2 for C=O, δ_C 71.7 and 70.2 for oxymethylenes and δ_C 135.8, 138.4, 134.3 and 143.9 for C-3, C-4, C-13 and C-14, respectively.

The *pro*-19*S* diastereotopic proton was ω-coupled ($^4J = 2.0$ Hz) with the H-6β proton, indicating α-axial orientation for C-19 (Bruno et al., 1981; Esquivel et al., 1986a,b; Stapel et al., 1980). The COSY spectrum clearly indicated that the proton at δ 7.14 (*t*, $J = 1.5$ Hz), assigned to H-14, was coupled with the oxymethylene protons at C-15. This triplet at δ 7.14 (H-14) was characteristic of a proton on the β-carbon of α-substituted butenolide ring (Muhammad et al., 1992). The HMBC spectrum which showed a ^3J correlation of CH_2-12 ($\delta_H = 2.24$ (*m*), 2.04 (*m*)) with C-16

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Table 1
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data along with important HMBC (^{2}J and ^{3}J) correlations of compounds **1** and **2**.

Position	**1** ($CDCl_3$)			**2** ($CDCl_3$)		
	δ_H (*m*, Hz)	δ_C	HMBC	δ_H (*m*, Hz)	δ_C	HMBC
1	1.77 (*m*), 1.07 (*m*)	19.5		1.76 (*m*), 1.08 (*m*)	19.5	
2	2.40 (*m*), 2.23 (*m*)	27.6		2.42 (*m*), 2.20 (*m*)	27.7/27.6	
3	6.76 (*dd*, 7.4; 2.0)	135.8	C-1, 2, 4, 5, 18	6.76 (*m*)	135.8/135.7	C-1, 2, 4, 5, 18
4		138.4			138.7	
5		45.5			45.5	
6	1.93 (*m*), 1.25 (*m*)	34.4		1.94 (*m*), 1.25 (*m*)	34.4	
7	1.62 (*m*), 1.51 (*m*)	27.7		1.65 (*m*), 1.50 (*m*)	27.7/27.6	
8	1.68 (*m*)	36.5	C-20	1.67 (*m*)	36.6	C-20
9		38.7			38.8	
10	1.75 (*m*)	48.0	C-1, 5, 8, 9, 11	1.73 (*m*)	48.1	C-1, 5, 8, 9, 11
11	1.60 (*m*)	35.2		1.60 (*m*)	35.02/34.96	
12	2.24 (*m*), 2.04 (*m*)	18.9	C-16	2.29 (*m*), 2.02 (*m*)	18.91/18.87	C-16
13		134.3			138.5/138.4	
14	7.14 (*t*, 1.5)	143.9	C-13, 15,16	6.79 (*m*)	141.6/141.5	C-12, 13, 15, 16
15	4.79 (*d*, 1.8).	70.2	C-13, 14, 16	5.74 (*m*)	102.5	C-13, 14, 16, 21
16		174.2			171.2	
17	0.86 (*d*, 6.6)	15.5	C-7, 8, 9	0.86 (*d*, 6.6) and 0.85 (*d*, 6.6)	15.5	C-7, 8, 9
18		169.3			169.3	
19	*pro-R* 4.30 (*d*, 8.1), *pro-S* 3.92 (*dd*, 8.0, 2.0)	71.7		*pro-R* 4.30 (*d*, 8.0), *pro-S* 3.92 (*dd*, 8.0, 2.0)	71.7	
20	0.62 (*s*)	17.5	C-9, 10	0.62 (*s*)	17.5	C-9, 10
OMe				3.58 (*s*)	57.2/57.1	C-15

(δ_C = 172.0) is consistent with α-substituted, rather than β-substituted, butenolide ring (Esquivel et al., 1986b, 1988; Faini et al., 1987).

The ^{13}C NMR signals (Table 1) at δ 17.5 and 15.5 were due to tertiary and secondary methyl groups at C-9 and C-8, respectively, being consistent with α-substitution for both methyl groups on a *trans*-clerodane skeleton (Givovich et al., 1986; Luteijn and De Groot, 1982; San-Martín et al., 1986; San-Martin et al., 1986; Sharma et al., 1984). Furthermore, in *trans*-clerodanes, C-20 resonates at higher field (δ 17–19) than in *cis*-clerodanes (δ 21–29) (Manabe and Nishino, 1986). In the ^{13}C NMR of compound **1** the C-20 carbon resonated at δ 17.5, supporting the *trans* geometry.

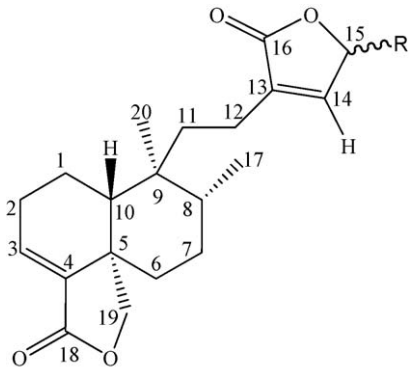
The relative configuration in compound **1** was further confirmed on the basis of a NOESY experiment which showed cross-peaks between CH_3-20 and CH_3-17, CH_2-19 and CH_3-20 and H-6β and H-10. These results are consistent with CH_3-20, CH_3-17, CH_2-19 being on the same face of the molecule and H-10 on the other face of the molecule.

The olefinic proton at C-3 (δ 6.76) showed HMBC cross-peaks with C-18 (δ 169.3), C-5 (δ 45.5), C-2 (δ 27.6) and C-1 (δ 19.5). The other olefinic proton at C-14 (δ 7.14) showed HMBC cross-peaks with C-16 (δ 174.2), C-15 (δ 70.2), C-13 (δ 134) allowing unequivocal assignment of these signals. Based on this data the first new compound (**1**) was identified as *neo*-clerodan-3,13-dien-16,15:18,19-diolide (Fig. 1) for which the trivial name mkapwanin, was suggested based on the Kiswahili name for *D. angustifolia* which is mkapwani. The *cis* isomer of this compound was recently reported from *Solidago virgaurea* (Starks et al., 2010).

Compound **2** was isolated as an epimeric mixture where some of the signals appeared as duplicate in the NMR spectra (Table 1). The HRMS of the epimeric mixture showed a molecular ion peak at *m*/*z* 360.8609 indicating the molecular formula $C_{21}H_{28}O_5$. The ^{1}H NMR and ^{13}C NMR spectra of **2** showed a similar signal pattern with that of **1**. However, the epimeric mixture differ from compound **1** by the presence of a methoxyl substituent at C-15 (δ_H = 3.58 and δ_C = 57.2/57.1) Furthermore, the presence of two methoxy signals in the ^{13}C NMR (δ_C = 57.2 and 57.1) confirmed the presence of an epimeric mixture. The methoxy protons (δ 3.58) showed HMBC correlations with C-15 (δ_C = 102.5) allowing its placement at C-15 which was confirmed from COSY and NOESY experiments. Thus the NOESY spectrum showed correlations of this group (OMe) with H-15 (δ 5.74) which in turn showed both COSY and NOESY correlation with H-14 (δ 6.79).

The proton at C-15 appeared downfield shifted at δ 5.74 consistent with it being attached to an acetal carbon with the corresponding carbon resonating at δ_C = 102.5. Furthermore, this proton was coupled with the multiplet at δ 6.79 (H-14) which in turn showed long-range allylic coupling with CH_2-12 (δ 2.29 and δ 2.02) as shown in the COSY spectrum. The substitution pattern at the lactone ring attached to C-12 was confirmed by HMBC correlation of H-15 with C-13 (δ 138.5/138.4), C-14 (δ 141.6), C-16 (δ 171.2) and the methoxyl at δ 57.2/57.1 (Table 1). The HMBC correlation of CH_2-12 with C-16 (C = O) is once again consistent with α-substituted butenolide ring. The epimeric mixture was therefore identified as 15-methoxy-*neo*-clerodan-3,13-dien-16,15:18,19-diolide (**2**) and the trivial name 15-methoxymkapwanin was assigned to this new compound (Fig. 1).

Diterpenoids with α-substituted butenolide moieties have not been isolated from *D. angustifolia* prior to this report. However, a compound with α-substituted butenolide ring, methyl dodovisate B, has been recently isolated from *D. viscosa* (Hong-Mei et al., 2010). Other plant species with such compounds include *Otostegia limbata* (Viqar et al., 2005), *Baccharis crispa* Sprengel (Juan et al., 1997) and *S. virgaurea* (Starks et al., 2010). It will be worthwhile to



1 R = H
2 R = OMe

Fig. 1. Structures of mkapwanin (**1**) and 15-methoxymkapwanin (**2**).

conduct directed investigation of *D. viscosa* and other *Dodonaea* species for the presence of these new compounds, in order to determine their chemotaxonomic values.

The other compounds isolated in this study were identified as flavonoids, a diterpenoid and a coumarin namely 5-hydroxy-3,7,4′-trimethoxyflavone (Dreyer, 1978); 5-hydroxy-3,6,7,4′-tetramethoxyflavone (Wollenweber et al., 1986); 3,5-dihydroxy-7,4′,-dimethoxyflavone (Dreyer, 1978); kumatakenin (Vieira et al., 1997; Sarmento da Silva et al., 2002); penduletin (Sachdev and Kulshreshtha, 1986); hautriwaic acid (Jefferies et al., 1973; Jefferies and Payne, 1967; Hsu et al., 1971); ayanin (Perez-Castorena et al., 1997; Jakobsen et al., 2001); rhamnocitrin (Wollenweber et al., 1986); kaempferol (Khan et al., 1992) and 7-hydroxy-6-methoxycoumarin (Andrianova et al., 1975).

3. Experimental

3.1. General

Analytical TLC was done using Merck pre-coated Silica gel 60 F_{254}. Column chromatography was carried out using Silica gel 60 (70–230 mesh) and Sephadex LH-20. EIMS spectra were recorded at 70 EV, on a SSQ 710 Finnigan MAT mass spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were run on a AVANCE-500 (Bruker). HMQC and HMBC spectra were acquired using standard Bruker software.

3.2. Plant material

The fresh leaves of *D. angustifolia* were collected from Voi, 300 km from Nairobi, on the 30th September, 2008, and identified by Mr. S.G. Mathenge of the University of Nairobi Herbarium, Department of Botany, where a voucher specimen (Mathenge-030/September 2008) is deposited.

3.3. Extraction and isolation

Fresh leaves (770 g) were extracted by successive dipping into fresh portions of acetone for short periods (*ca.* 15 s) to yield (100 g, 13%) of a gummy extract after evaporation of the solvent under reduced pressure. A portion of the crude extract (52 g) was subjected to column chromatography on Silica gel (520 g) eluting with mixtures of *n*-hexane/CH_2Cl_2 and then with CH_2Cl_2/MeOH in increasing order of polarities. Yellow crystals of 5-hydroxy-3,7,4′-trimethoxyflavone (206 mg) precipitated out of the fraction eluted with 50% CH_2Cl_2 in *n*-hexane. The mother liquor was purified by column chromatography on Sephadex LH-20 (eluting with CH_2Cl_2/MeOH, 1:1) to yield 5-hydroxy-3,6,7,4′-tetramethoxyflavone (46 mg) and 3,5-dihydroxy-7,4′,-dimethoxyflavone (36 mg). The fraction eluted with 60% CH_2Cl_2 in *n*-hexane afforded crystals of kumatakenin (50 mg). The mother liquor was separated by PTLC (Silica gel; multiple development; *n*-hexane/CH_2Cl_2, 1:1) to give yellow crystals of penduletin (108 mg). White crystals of hautriwaic acid (1.53 g) precipitated out of the fraction eluted with 100% CH_2Cl_2. The mother liquor of this fraction was concentrated *in vacuo* and set for recrystallization, to yield a second crop of hautriwaic acid (277 mg). The fraction eluted with 1% MeOH in CH_2Cl_2 after purification by PTLC (Silica gel) in the same solvent system, with multiple development, afforded ayanin (12 mg). The mother liquor of this fraction was purified by PTLC developing severally in 100% CH_2Cl_2 to yield 7-hydroxy-6-methoxycoumarin (22 mg) as the major band. The fraction eluted with 2% MeOH in CH_2Cl_2 after purification by column chromatography using Sephadex LH-20 (solvent system CH_2Cl_2/MeOH, 1:1) and preparative TLC (solvent system 1% MeOH in CH_2Cl_2; two developments) afforded *neo*-clerodan-3,13-dien-16,15:18,19-diolide (**1**) (60 mg), 15-methoxy-*neo*-clerodan-3,13-dien-16,15:18,19-diolide (**2**) (156 mg). The fraction eluted with 3% MeOH in CH_2Cl_2 after purification by column chromatography using sephadex LH-20 (solvent system CH_2Cl_2/MeOH; 1:1) yielded rhamnocitrin (33 mg) and kaempferol (57 mg).

3.4. *neo*-Clerodan-3,13-dien-16,15:18,19-diolide (mkapwanin, 1)

Colourless oil (CH_2Cl_2 – *n*-hexane), R_f 0.2 (1% MeOH in CH_2Cl_2); $[\alpha]_D^{27} = -11.7$ (*c*, 0.05, CH_2Cl_2); % yield 0.04; ^{1}H NMR and ^{13}C NMR (Table 1); EIMS *m*/*z* (rel. int.): 330 (13, $[M]^+$), 300 (13, $[M\text{-}CH_2O]^+$), 219 (53, $[C_{14}H_{19}O_2]^+$), 189 (100), 161 (15), 105 (20), 91 (30), 84 (28). HR-EIMS: *m*/*z* = 331.1894 ($[C_{20}H_{26}O_4+H]^+$; calc. 331.4260).

3.5. 15-Methoxy-*neo*-clerodan-3,13-dien-16,15:18,19-diolide (15-methoxymkapwanin, 2)

Colourless oil (CH_2Cl_2 – *n*-hexane); R_f 0.1 [1% MeOH in CH_2Cl_2]; $[\alpha]_D^{27} = -50.3$ (*c*, 0.34, CH_2Cl_2); % yield 0.06; ^{1}H NMR and ^{13}C NMR (Table 1). EIMS *m*/*z* (rel. int.): 361 (25, $[MH]^+$), 342 (18, $[M\text{-}H_2O]^+$), 330 (36, $[CH_2O]^+$), 329 (54, $[CH_3O]^+$), 310 (52), 283 (52), 189 (32), 91 (43), 86 (59), 84 (100). HR-EIMS: *m*/*z* = 360.8609 ($[C_{21}H_{28}O_5]^+$; calc. 360.4440).

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