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Iridoids from *Kigelia pinnata* DC. fruits

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Abstract

From the fruits of *Kigelia pinnata* DC., a new furanone derivative formulated as 3-(2′-hydroxyethyl)-5-(2″-hydroxypropyl)-dihydrofuran-2(3H)-one (**1**), and four new iridoids named; 7-hydroxy viteoid II (**2**), 7-hydroxy eucommic acid (**3**), 7-hydroxy-10-deoxyeucommiol (**4**) and 10-deoxyeucommiol (**5**) have been isolated together with seven known iridoids, jiofuran (**6**), jioglutolide (**7**), 1-dehydroxy-3,4-dihydroaucubigenin (**8**), des-*p*-hydroxybenzoyl kisasagenol B (**9**), ajugol (**10**), verminoside (**11**) and 6-*trans*-caffeoyl ajugol (**12**). The structures of the isolated compounds were characterized by different spectroscopic methods.

Keywords: *Kigelia pinnata* DC.; Bignoniaceae; Iridoids; Furanone derivative

1. Introduction

Kigelia pinnata DC. (syn. *Kigelia africana* Benth) belongs to the family Bignoniaceae is an African tree growing in the tropics (Hutchinson and Daziel, 1963; Burkill, 1985). In the folk medicine, the fruits of the plant are used as dressing for ulcers, purgative and to increase the flow of milk in lactating women (Oliver-Bever, 1986). The bark is traditionally used as a remedy for syphilis and gonorrhea (Watt and Breyer-Brandwijk, 1962). Some interesting diverse biological studies on *K. pinnata* had been reported such as the anti-implantation (Prakash et al., 1985), molluscicidal (Kela et al., 1989), and antimicrobial (Akunyili et al., 1991) activities. The extracts of the stem-bark and fruit were screened for their cytotoxic activities and showed promising results against melanoma and renal carcinoma (Houghton et al., 1994), while the root-bark showed activity against KB cells (Weiss et al., 2000). Reviewing the current literature revealed the isolation of naphthoquinons (Inoue et al., 1981; Akunyili and Houghton, 1993; Weiss et al., 2000), coumarins (Govindachari et al., 1971), iridoids (Houghton and Akunyili, 1993) and flavonoids (El-Sayyad, 1982).

Herein we report the isolation and structural elucidation of a new furanone derivative; 3-(2′-hydroxyethyl)-5-(2″-hydroxypropyl) dihydro-furan-2(3H)-one (**1**) together with four new iridoids; 7-hydroxy viteoid II (**2**), 7-hydroxy eucommic acid (**3**), 7-hydroxy-10-deoxyeucommiol (**4**) and 10-deoxyeucommiol (**5**), in addition to seven known iridoids on the basis of extensive NMR studies.

2. Results and discussion

All compounds (**1**–**12**) were obtained from the methanolic extract of the air-dried powdered fruits of *K. pinnata* DC. as described in the Experimental Section.

Compound **1** exhibited a molecular formula $C_9H_{16}O_4$ from its negative ion HR FAB–MS (Experimental section). The ^{13}C and DEPT ^{13}C NMR spectral data (Table 1) revealed the presence of nine signals. The chemical shift value of C-5 at δ_c 84.5 and the carbonyl signal at δ_c 179.2 indicated the presence of a γ-lactone (Breitmaier and Voelter, 1987), and the remaining structure was elucidated by the aid of its 2D NMR spectral data including ^1H–^1H COSY (Table 1). Further confirmation was achieved by HMBC experiment (Fig. 1), where correlations were observed between C-2 with H-1′ and H-4, C-4 with H-1″ and H-1′ and C-2′

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Table 1
^{13}C (100 MHz) and ^{1}H NMR (400 MHz) spectral data of compound **1** in CD_3OD

C	δ_C	H	δ_H	Multiplicity	^{1}H–^{1}H COSY
2	179.2 *s*		–	–	
3	40.0 *d*	**3**	2.28	1H, *m*	H-4, H-1′
4	36.0[a] *t*	**4**	2.37	1H, *m*	H-3, H-5
			2.70	1H, *m*	H-3, H-5
5	84.5 *d*	**5**	4.40	1H, *m*	H-4, H-1″
1′	36.1[a] *t*	**1′**	1.78	1H, *m*	H-3, H-2′
			1.56	1H, *m*	H-3, H-2′
2′	60.9 *t*	**2′**	3.59	2H, *m*	H-1′
1″	44.9 *t*	**1″**	1.73	1H, *m*	H-5, H-2″
			1.69	1H, *m*	H-5, H-2″
2″	65.3 *d*	**2″**	3.92	1H, *m*	H-1″, H-3″
3″	24.3 *q*	**3″**	1.19	3H, *d*, $J=6.3$	H-2″

The coupling constant (J) values in Hz.
[a] Chemical shift values may be interchangeable.

Table 2
^{13}C NMR (100 MHz, CD_3OD) spectral data of compounds **2**–**5**

C	**2**	**3**	**4**	**5**
1	166.1 *s*	56.8 *t*	57.2 *t*	57.0 *t*
3	70.9 *t*	175.1 *s*	62.0 *t*	61.8 *t*
4	28.7 *t*	36.1 *t*	35.1 *t*	35.2 *t*
5	47.8 *d*	52.2 *d*	49.9 *d*	53.7 *d*
6	78.5 *d*	76.7 *d*	77.4 *d*	76.8 *d*
7	74.0 *d*	75.8 *d*	79.0 *d*	46.9 *t*
8	159.5 *s*	139.9 *s*	136.6 *s*	134.7 *s*
9	127.5 *s*	142.6 *s*	139.8 *s*	136.4 *s*
10	58.6 *t*	57.4 *t*	11.7 *q*	14.0 *q*

with H-3. On the basis of these above mentioned data, the structure of **1** was determined to be 3-(2′-hydroxyethyl)-5-(2″-hydroxypropyl) dihydrofuran-2(3H)-one.

The molecular formula of compound **2** was determined to be $C_9H_{12}O_5$ from its negative ion HR FAB–MS (Experimental section) and its ^{13}C NMR data (Table 2). The ^{13}C NMR including DEPT mode measurements of **2** showed signals corresponding to one carbonyl, two olefinics, three methines, two methylenes and one hydroxymethyl assuming the presence of C-9 iridoid derivative (Ono et al., 1997). The ^{1}H NMR resonances (Table 3) were assigned on the basis of HSQC and ^{1}H–^{1}H COSY. In the later, a proton doublet at δ_H 4.55 (1H, d, $J=5.9$ Hz, H-7) was coupled to a proton at δ_H 3.72 (1H, dd, $J=7.1$, 5.9 Hz, H-6) which in turn was coupled to a proton at δ_H 2.97(1H, m, H-5). In addition, H-5 showed a cross peaks with H-4 (δ_H 2.28 and 1.64, each 1H, m) which showed also cross peaks with H-3 (δ_H 4.44, 1H, dd, $J=4.6$, 2.9 Hz and 4.37, 1H, dd, $J=6.1$, 3.4 Hz). The position of the double bond was assigned to be between C-8 and C-9 due to the resonance of H-7 as a doublet signal in the ^{1}H NMR spectrum and proved by HMBC correlation of C-8 with H-5 and H-7 and correlation between C-9 with H-4, H-5 and H-7 (Fig. 2). The position of the hydroxymethyl group (C-10) was proved also by the HMBC correlation peaks between both C-7 and C-9 with H-10. The NMR spectral data of **2** agreed with those of viteoid II, previously isolated from *Vitex rotundifolia* L. (Ono et al., 1997) except for the presence of an additional hydroxyl group attached to C-7. The presence of a correlation

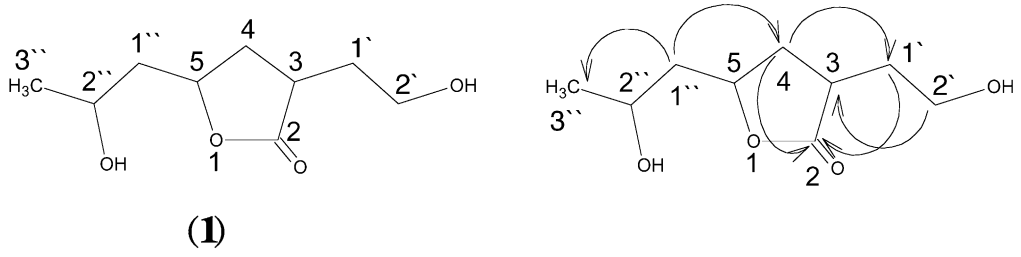

Fig. 1. HMBC correlations of (**1**).

Fig. 2. HMBC and NOESY correlations of (**2**).

Table 3
^{1}H NMR[a] (400 MHz, CD_3OD) spectral data of compounds **2**–**5**

H	2	3	4	5
1		4.16, 1H, *d* (13.2) 4.01, 1H, *d* (13.2)	4.11, 1H, *d* (12.5) 3.94, 1H, *d* (12.5)	4.19, 1H, *d* (12.2) 4.03, 1H, overlapped with H-6
3	4.37, 1H, *dd* (6.1, 3.4) 4.44, 1H, *dd* (4.6, 2.9)		3.60, 2H, *t* (6.8)	3.66, 2H, *t* (6.8)
4	2.28, 1H, *m* 1.64, 1H, *m*	2.59, 1H, *dd* (15.6, 5.6) 2.30, 1H, *dd* (15.6, 8.3)	1.86, 1H, *m* 1.34, 1H, *m*	1.89, 1H, *m* 1.41, 1H, *m*
5	2.97, 1H, *m*	3.00, 1H, *m*	2.59, 1H, *m*	2.63, 1H, *m*
6	3.72, 1H, *dd* (7.1, 5.9)	3.76, 1H, *t* (5.4)	3.73, 1H, *dd* (5.6, 4.2)	4.03, 1H, *m*
7	4.55, 1H, *d* (5.9)	4.45, 1H, *br.d* (5.4)	4.16, 1H, *br.d* (5.6)	2.17, 1H, *br.d* (16.6) 2.63, 1H, *m*
10	4.41, 1H, *d* (15.9) 4.99, 1H, *d* (15.9)	4.19, 1H, *d* (12.4) 4.06, 1H, *d* (12.4)	1.64, 3H, *s*	1.70, 3H, *s*

[a] Chemical shifts in ppm, *J* values in parentheses are recorded in Hz.

between H-6 and H-7 with the lack of a similar correlation between H-5 and H-6 in the NOESY experiment (Fig. 2) and by comparison with viteoid II (Ono et al., 1997), the β-configuration of H-5 and hydroxyl groups of C-6 and C-7 were determined. Based on the above mentioned data, compound **2** was assigned as 7-hydroxy viteoid II.

The molecular formula of compound **3** was assigned as $C_9H_{14}O_6$ on the basis of negative ion HR FAB–MS (Experimental section) and ^{13}CNMR spectra (Table 2). In the ^{1}H and ^{13}C NMR spectral data of **3** (Tables 2 and 3), the signal patterns were similar to those of 7-hydroxy eucommic acid *n*-butyl ester, isolated from *Catalpa* species (Machida et al., 2001), except for the absence of the *n*-butyl group suggesting the structure of **3** to be 7-hydroxy eucommic acid. This structure was confirmed through the analysis of its ^{1}H–^{1}H COSY and HMBC, the later showed correlation between C-3 and H-5, C-9 with both H-4 and H-7 and between C-8 with both H-1 and H-5 (Fig. 3). From the results of NOESY experiment, the relative stereochemistry at C-5, C-6 and C-7 were similar to those of **2** where a correlation was observed between H-6 and H-7 with the absence of a similar correlation between H-5 and H-6 (Fig. 3). This is the first report about the isolation of this compound in the form of a free acid from a natural source.

Compound **4** exhibited a molecular formula $C_9H_{16}O_4$ from its negative ion HR FAB–MS (Experimental section). The ^{13}C NMR and DEPT spectral data (Table 2) suggested **4** to be a C-9 iridoid (Bianco et al., 1981). The ^{13}C and ^{1}H NMR spectral data of **4** (Tables 2 and 3) were similar to those of eucommiol isolated from *Aucuba japonica* (Bernini et al., 1984), except for lacking the signals due to the hydroxymethyl group at C-8 and instead, showed signal characteristic for a methyl group at δ_H 1.64 (3H, s) with δ_c 11.7 (C-10). Furthermore, a signal at δ_c 79.0 assignable to the hydroxylated methine C-7 with δ_H 4.16 (1H, *br.d*, $J = 5.6$ Hz, H-7) was observed. The singlet methyl (H-10) and the AB doublet of the hydroxymethyl signal (H-1) indicated the position of the double bond between C-8 and C-9. The structure was confirmed by the aid of HSQC and ^{1}H–^{1}H COSY where the proton H-6 at δ_H 3.73 (1H, *dd*, $J = 4.2$ and 5.6 Hz) was coupled to protons H-7 at δ_H 4.16 (1H, *br.d*, $J = 5.6$ Hz) and H-5 at δ_H 2.59 (1H, m) also, the methylene protons H-4 at δ_H 1.86 and 1.34 (each 1H, *m*) were coupled to H-3 at δ_H 3.60 (2H, *t*, $J = 6.8$ Hz) and H-5. Consequently, compound **4** was determined as 7-hydroxy-10-deoxyeucommiol. The NOESY experiment of **4** (Fig. 4) showed similar correlations as those of **2** and **3** confirming the β-configuration of H-5 and the hydroxyl groups at C-6 and C-7.

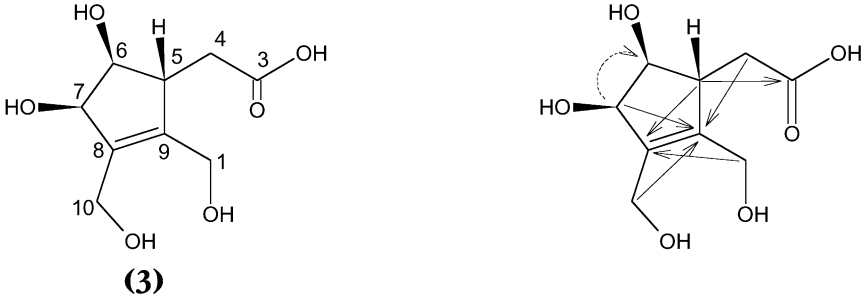

Fig. 3. HMBC and NOESY correlations of (**3**).

Fig. 4. NOESY correlation of (**4**).

Fig. 5. HMBC correlations of (**5**).

The molecular formula of compound **5** was determined as $C_9H_{16}O_3$ from the negative ion HR FAB–MS (Experimental section). The ^1H and ^{13}C NMR data of **5** (Tables 2 and 3) were similar to those of **4** except for the presence of methylene carbon signal at δ_c 46.9 (C-7) instead of the hydroxymethine signal at δ_c 79.0 of **4**. So, the structure of **5** was assumed to be 10-deoxy-eucommiol. This assignment was confirmed by ^1H–^1H COSY, HSQC and HMBC analysis. In the later (Fig. 5), correlations were observed between C-5 and the hydroxymethyl protons (H-1) and between C-7 and the methyl protons (H-10). The β-orientation of H-5 and the hydroxyl group at C-6 was suggested by comparison with those reported for the same synthesized compound (Bianco et al., 1981).

The known iridoids; jiofuran (**6**) (Morota et al., 1989), jioglutolide (**7**) (Morota et al., 1989), 1-dehydroxy-3,4-dihydroaucubigenin (**8**) (Kajimoto et al., 1989), des-*p*-hydroxybenzoyl kisasagenol B (**9**) (Machida et al., 1998), ajugol (**10**) (Nishimura et al., 1989; Kaneko et al., 1997), verminoside (**11**) (Sticher et al., 1979 and Houghton and Akunyili, 1993) and 6-*trans*-caffeoyl ajugol (**12**) (Liva et al., 2001) were identified by means of different techniques of NMR spectral analysis and by comparison of their data with those reported in the literature.

3. Experimental

General: Mps are uncorr. Optical rotations were measured on Union PM-101 automatic digital polarimeter. HR FAB–MS were recorded with JEOL JMS-SX 102 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were measured on JEOL JNM A400 spectrophotometer (400 and 100 MHz, respectively) using TMS as an internal standard. Column chromatography was performed on Kieselgel 60 (60–230 mesh, Merck), Lichroprep RP-18 (Merck) and Diaion HP-20 (Mitsubishi). Preparative HPLC was carried out on a column of ODS (150×20 mm i.d., YMC) with JASCO PU-1580 Pump, JACSO UV-975 UV/visible detector and TOYO SODA RI-8000 refractive index detector. TLC was carried out with silica gel 60 precoated plates F-254s.

3.1. Plant material

The fruits of *K. pinnata* DC. were collected from Aswan Botanical Garden, Aswan, Egypt, in October 1999. The plant was kindly identified by Prof. Dr. Naeem El-Keltawy, Prof. of Horticulture, Faculty of Agriculture, Assiut University, Assiut, Egypt. A voucher sample was kept in the Herbarium of Pharmacognosy Department, Faculty of Pharmacy, Assiut University, Assiut, Egypt.

3.2. Extraction and isolation

The air-dried powdered fruits of *K. pinnata* DC. (3.3 kg) was exhaustively extracted with methanol at room temperature. The methanolic extract was concentrated under reduced pressure till dryness. The residue (460 g) was suspended in water and extracted with diethyl ether.

The aqueous layer, after evaporation to a minimum volume, was subjected to a Diaion HP-20 CC and eluted with water, 50% MeOH, MeOH and finally with acetone. The residue of 50% MeOH eluate (21 g) was subjected to a silica gel CC using EtOAc–MeOH–H_2O (90:10:0 to 60:40:10) gradient as eluting systems to give four fractions (Fractions I, II, III and IV). The eluted fractions were monitored on silica gel TLC with CH_2Cl_2–MeOH–H_2O (8:2:0.2) as a solvent system and RP with 20%, 30%, 40% MeOH, 20% and 30% MeCN as solvent systems.

Fraction II (9 g) was chromatographed on RP-18 CC using 10–50% MeOH gradient as solvent systems, where seven fractions were obtained (Fr.-1–Fr.-7). The first fraction (Fr.-1, 1.2 g) was subjected to a silica gel CC using EtOAc–MeOH–H_2O (95:5:0 to 80:20:2) as solvent systems to yield seven subfractions (Fr.-1-1–Fr.-1-7). Fr.-1-3 (164 mg) was chromatographed on prep. HPLC using 10% MeOH as a mobile phase where compounds **1** (14 mg) and compound **8** (10 mg) were obtained. Fr.-1-4 (230 mg) was subjected to prep. HPLC using 15% as a solvent system where compound **2** (20 mg) and compound **9** (12 mg) were obtained. Fr.-1-6 (162 mg) was chromatographed on prep. HPLC and eluted with 15% MeOH to give compounds **3** (28 mg) and **4** (18 mg). Fr.-1-1 (40 mg) was subjected to prep. HPLC using 10% MeOH as a mobile phase, where compound **6** (10 mg) was obtained. Fr.-1-2 (72 mg) was subjected to prep. HPLC using 15% MeOH as a mobile phase to give compound **7** (21 mg). Fr.-1-7 (70 mg) was subjected to prep. HPLC using 10% MeOH to give compound **10** (20 mg). The second fraction (Fr.-2, 630 mg) was chromatographed on a silica gel CC and eluted with CH_2Cl_2–MeOH (92:8 to 85:15) gradient followed by prep. HPLC using 18% MeOH to give compound **5** (45 mg). The fifth fraction (Fr.-5, 1.6 g) was subjected to silica gel CC eluted with CH_2Cl_2–MeOH–H_2O (95:5:0 to 80:20:2) followed by prep. HPLC using 45% MeOH as mobile phase to give compound **11** (187 mg). The sixth fraction (Fr.-6, 300 mg) was subjected to prep. HPLC using 40% MeOH as a mobile phase to afford compound **12** (114 mg).

3.2.1. Compound (1)

3-(2′-Hydroxyethyl)-5-(2″-hydroxypropyl)-dihydrofuran-2(3H)-one (**1**): yellow oil, $[\alpha]_D^{23} = +77.94^\circ$ (*c* 1.36, MeOH). Molecular formula $C_9H_{16}O_4$. Negative HR FAB–MS *m/z*: 187.0950 $[M-H]^-$ $C_9H_{15}O_4$ (req. 187.0970). ^{13}C and ^1H NMR (Table 1).

3.2.2. Compound (2)

7-Hyrdroxy viteoid II (**2**): yellowish-brown oil. $[\alpha]_D^{17} = -76.14^\circ$ (*c* 0.66, MeOH). Molecular formula $C_9H_{12}O_5$. Negative HR FAB–MS *m/z*: 199.0603 $[M-H]^-$ $C_9H_{11}O_5$ (req. 199.0607). ^{13}C and ^1H NMR (Tables 2 and 3).

3.2.3. Compound (3)

7-Hydroxy eucommic acid (**3**): yellowish-brown powder. $[\alpha]_D^{17} = -73.16^\circ$ (*c* 1.45, MeOH). Molecular formula $C_9H_{14}O_6$. Negative HR FAB–MS *m/z*: 217.0716 $[M-H]^-$ $C_9H_{13}O_6$ (req. 217.0712). ^{13}C and ^1H NMR (Tables 2 and 3).

3.2.4. Compound (4)

7-Hydroxy-10-deoxyeucommiol (**4**): yellow oil. $[\alpha]_D^{17} = -53.44^\circ$ (*c* 1.06, MeOH). Molecular formula $C_9H_{16}O_4$. Negative HR FAB–MS *m/z*: 187.0959 $[M-H]^-$ $C_9H_{15}O_4$ (req. 187.0970). ^{13}C and ^1H NMR (Tables 2 and 3).

3.2.5. Compound (5)

10-Deoxyeucommiol (**5**): yellow oil. $[\alpha]_D^{17} = -33.77^\circ$ (*c* 3.61, MeOH). Molecular formula $C_9H_{16}O_3$. Negative HR FAB–MS *m/z*: 171.1002 $[M-H]^-$ $C_9H_{15}O_3$ (req. 171.1021). ^{13}C and ^1H NMR (Tables 2 and 3).

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