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STILBENOIDS FROM LEAVES OF *UPUNA BORNEENSIS*

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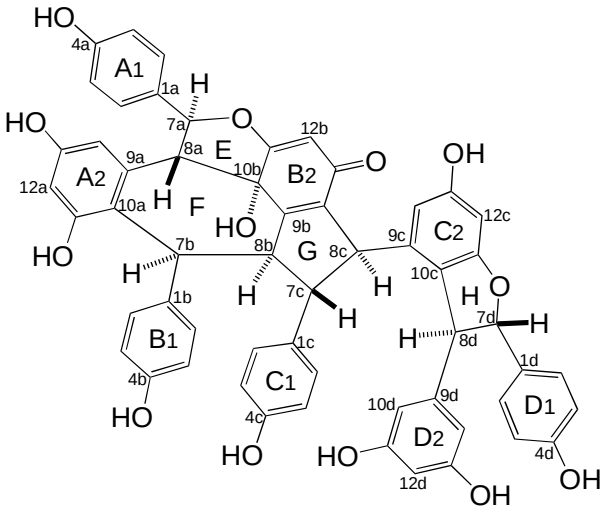
Abstract - An acetone extract of the leaves of *Upuna borneensis* afforded two stilbene tetramer derivatives (upunaphenols F and G) together with four stilbenoids (vaticanols B and C, piceid and *cis*-piceid). The structures and their relative stereochemistry were determined by spectroscopic techniques, in particular by using 2D NMR method. Upunaphenol G was found to suppress cell growth in HL60 cells with IC_{50} at 15.6 μM.

INTRODUCTION

Dipterocarpaceous plant have been shown to be rich in resveratrol oligomers.[1] In continuation of our study to search the chemical constituents with bioactive potency from Dipterocarpaceous plants, the chemical constituents (resveratrol oligomers) in some plants of *Vatica*,[2] *Shorea*,[3] *Vateria*[4] and *Dipterocarpus*[5] were characterized. In our previous studies, we have also examined some constituents in the stem of *Upuna borneensis* (Dipterocarpaceae),[6] which is a monotypic genus and rare species endemic to Indonesia.[7] Most of the previous phytochemical investigation of the family have been focused on the chemical constituents in stem (bark or wood). In the present study, stilbene oligomers in the leaves of *U. borneensis* were examined. We initiated this study, targeting on leaves of this family, in order to discover bioactive constituent and to find alternate material containing known bioactive stilbene oligomers, e.g. vaticanols B and C.[8, 9]

RESULTS AND DISCUSSION

Upunaphenols F (**1**) ($[\alpha]_D^{25}$ +5.6˚) and G (**2**) ($[\alpha]_D^{25}$ –62.1˚) were purified from an acetone-soluble part of



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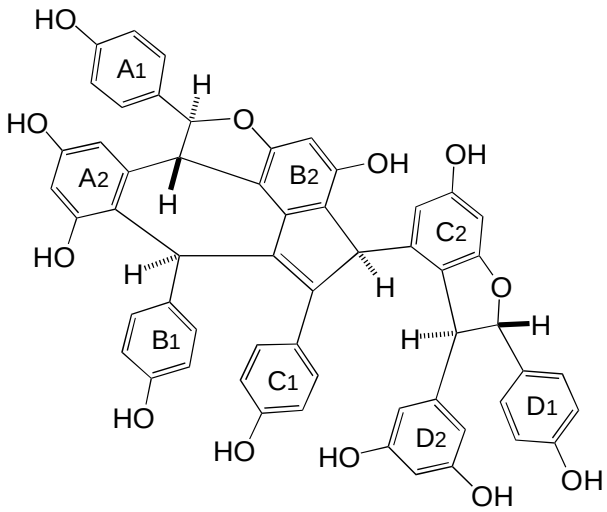

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leaves of *U. borneensis* by column chromatography over ODS, Sephadex LH-20 and preparative TLC. Two known resveratrol tetramers, vaticanols B (**3**) and C (**4**) and two known resveratrol monomers, piceid (**5**) and *cis*-piceid (**6**) were also isolated from the extract and the structures were identified by spectral comparison with the authentic samples (**3**–**5**)[2] and by the literature value (**6**).[10]

Upunaphenol F (**1**), obtained as a pale yellow amorphous solid, showed a positive reaction with the Gibbs reagent. The composition of **1** was deduced to be $C_{56}H_{42}O_{13}$ from the pseudo-molecular ion peak of $[M-H]^-$ at *m/z* 921.2565 in the HR–FAB–MS spectrum and the ^{13}C NMR spectrum which showed 56 carbon signals. A band in the IR spectrum at 1665 cm^{-1} and a signal in the ^{13}C NMR spectrum (δ_C 185.8) showed the presence of a α,β-unsaturated carbonyl group (C-13b) in the molecule. The ^1H and ^{13}C NMR spectral data of **1** (Table 1) together with ^1H–^1H COSY, ^{13}C–^1H COSY and HMBC spectrum indicated the presence of seven oxygenated aromatic rings which form four 4-hydroxyphenyl groups (rings A_1–D_1), two 1,2,3,5-tetrasubstituted benzene rings (rings A_2 and C_2) and a 3,5-dihydroxyphenyl group (ring D_2). The ^1H NMR spectrum (measured in DMSO-d_6, Table 1) exhibited clear signals of ten hydroxyl groups [δ 6.05 (br s, alcoholic-OH at C-10b); 8.95–9.62 (9 x OH)] which disappeared upon addition of D_2O. The spectrum also exhibited two sets of mutually coupled aliphatic protons (H-7a/H-8a and H-7d/H-8d) and a sequence of four aliphatic protons in this order (H-7b/H-8b/H-7c/H-8c). A proton signal (H-12b) was further observed. In the HMBC spectrum (Table 2), significant ^3J correlations were observed between H-7a/C-2a(6a), H-8a/C-14a, H-7b/C-11a, H-7b/C-2b(6b), H-7c/C-2c(6c), H-8c/C-14c, H-7d/C-2d(6d), H-8d/C-10d(14d) and H-8d/C-11c, which supported the connections between C-7a/C-1a, C-8a/C-9a, C-7b/C-10a, C-7b/C-1b, C-7c/C-1c, C-8c/C-9c, C-7d/C-1d, C-8d/C-9d and C-8d/C-10c, respectively. A

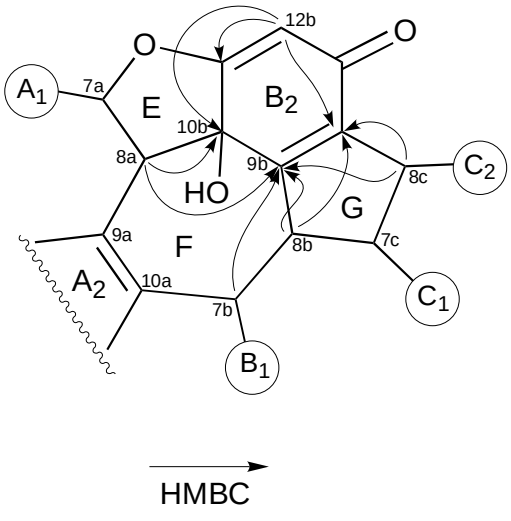

Figure 1 Selected HMBC correlations in **1**

cross peak observed between H-7d/C-11c supported the presence of an ether linkage (C-7d/O/C-11c), which formed dihydrobenzofuran ring (ring H: C-7d/C-8d/C-10c/C-11c/O). The remaining ring system and the connectivity in the molecule is determined as follows. The presence of a six-membered ring system was apparent from the signals of C-9b–C-14b in the ^{13}C NMR spectrum (Table 1). The ring was comprised of four quaternary sp^2 carbons [δ_C 155.3, 178.9, 185.8 (carbonyl), 140.2], one oxygenated quaternary carbon (δ_C 72.7), and a protonated sp^2 carbon (δ_C 99.0). The established partial structures of seven aromatic rings (rings A_1–D_1, A_2, C_2 and D_2) and the dihydrobenzofuran ring (ring H) account for 29 of the 36 required degrees of unsaturation. The presence of the carbonyl group and further signals for four sp2 signals in the ring B_2 suggested that the ring formed a cyclohexa-2,5-dienone ring and fused tetracyclic ring system. The important correlations of HMBC measurements for the fused cyclic system of the rings B_2, E, F and G were as follows (Figure 1); H-7b/C-9b, H-8b/C-14b and H-8c/C-9b for the connection of four carbons of C-8b, C-9b, C-14b and C-8c in this order; H-8a/C-9b for the C-C bond of C-8a/C-10b. Remaining oxygen could be allotted to the ether linkage (C-7a/O/C-11b) after considering the molecular formula. The planar structure of upunaphenol F was concluded to be **1**. The other correlations in the HMBC spectrum, as summarized in Table 2, were in accordance with this proposed planar structure. The planar structure of **1** was similar to those of vaticanol B (**3**) except for the structure of the ring B_1.

The stereostructure of **1** was determined by the result of NOESY experiment. In this experiment [Figure 2 (selected) and Table 2 (total)], the NOEs [H-7a/H-14a, H-8a/H-2a(6a), H-7d/H-10d(14d), H-8d/H-2d(6d) and H-8a/H-2b(6b)] suggested that the orientation of the protons on the rings E and H (H-7a/H-8a and H-

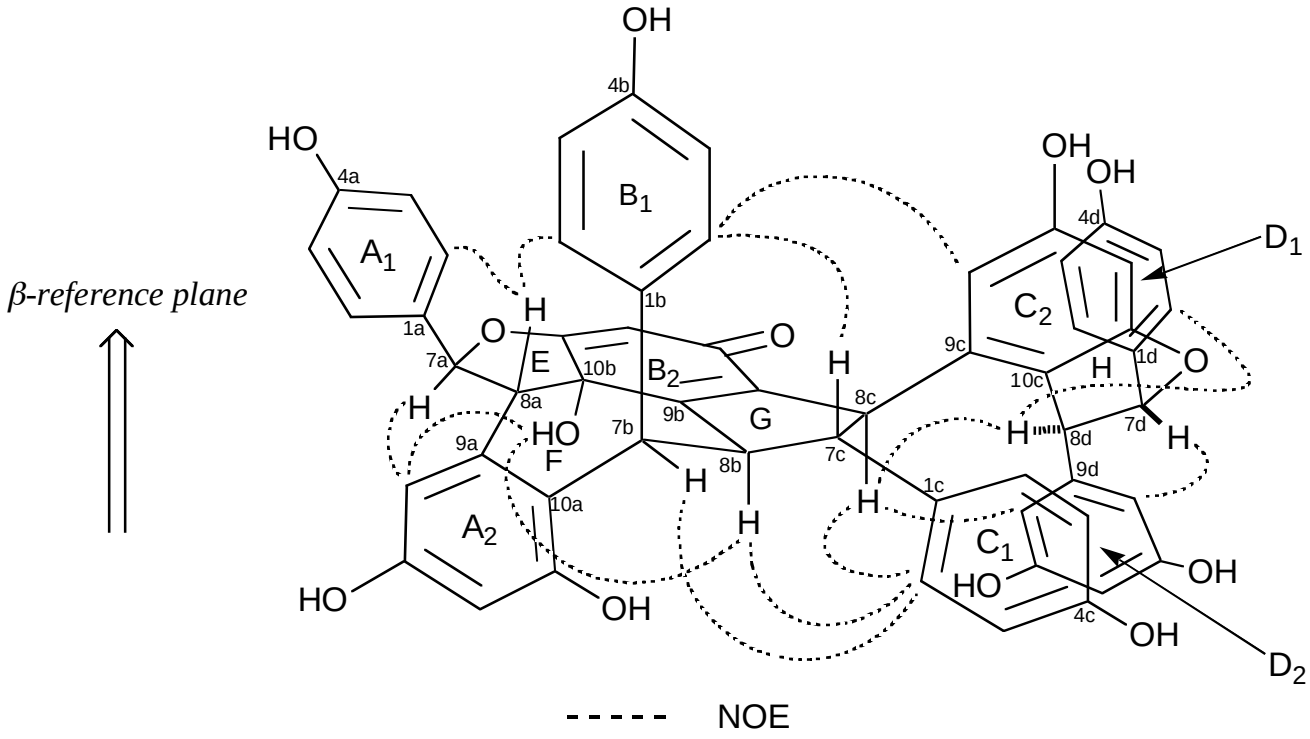

Figure 2 Relative structure and selected NOESY correlations in **1**

7d/H-8d) are *trans* and that the ring B_1 has a same orientation as H-8a (β-configuration). The aromatic protons on the ring C_1 [H-2c(6c)] showed NOEs with four methine protons (H-7b, H-8b, H-7c and H-8c), which can be observed only when H-7b, H-8b and H-8c are situated in *cis* toward the ring C_1 (α-configuration). The configuration of OH-10b was confirmed to be α by the NOEs of H-14a/OH-10b and H-8b/OH-10b. On the basis of these results, the relative structure of upunaphenol F was characterized as **1**, where all the methine protons are oriented in the same as those of **3**.

Upunaphenol G (**2**), obtained as a yellow amorphous powder, the molecular formula of $C_{56}H_{40}O_{12}$ was established by the HR–FAB–MS spectrum ($[M-H]^-$ ion at *m/z* 903.2449). The UV spectrum (310 nm) revealed the presence of a conjugated system in the structure. The presence of eight oxygenated aromatic rings (rings A_1–D_1 and rings A_2–D_2) and two sets of mutually coupled aliphatic protons (H-7a/H-8a and H-7d/H-8d) were exhibited by the analysis of ^1H and ^{13}C NMR spectral data of **2** (Table 1). The NMR spectral data also disclosed the presence of two methine protons (H-7b and H-8c) and two olefinic carbons (C-8b and C-7c). Analysis of ^3J long-range correlations in the HMBC spectrum (Table 2) confirmed the connection of all the partial structures to be **2**, which composed of four resveratrols A–D. The relative stereostructure of **2** was determined by NOESY spectrum as shown in Table 2. By the same reason as described in **1**, the *trans* orientation of the rings E and H and β-configuration of the rings B_1 and C_2 (H-7b, H-8c: α-configuration) were confirmed. The structure of **2** was structurally related to **3**, except that the methine carbons of C-8b and C-7c were reduced.

Compounds (**1–3)**, all of which bear a fused pentacyclic ring system, were examined for the cell growth assay in HL60 cells. Compounds (**2** and **3)** showed the growth suppression with IC_{50} values at 15.6 μM and 4.8 μM,[8] respectively, while compound (**1)** did not show the suppressive effect.

EXPERIMENTAL

General method

The following instruments were used: FAB–MS spectra, JEOL JMS-DX-300 instrument; ^1H and ^{13}C NMR spectra, JEOL JNM LA-300 (TMS as internal standard); UV spectra, Shimadzu UV-2200 spectrophotometer (in methanol solution); IR spectra, JASCO FT-IR 410 spectrometer (as KBr pellet); optical rotations, JASCO P-1020 polarimeter (in methanol solution). The following adsorbents were used for purification: analytical and preparative TLC, Merck Kieselgel 60 F_{254} (0.25 mm); column chromatography, Pharmacia Fine Chemicals AB Sephadex LH-20 and Fuji Silysia Chemical Chromatorex. The *in vitro* cell growth suppression assay was carried out according to procedures described in previously.[8]

Plant material

Upuna borneensis that was identified by one of the co-authors (D.D.) was cultivated at Bogor Botanical Garden, Bogor, Indonesia, where several leaves were collected in May 2000. A voucher specimen has been deposited in Gifu Prefectural Institute of Health and Environmental Sciences, Gifu, Japan.

Extraction and isolation

The dried and ground leaves (1.4 Kg) of *U. borneensis* was extracted successively with acetone (8 L x 24

Table 1 ^{1}H and ^{13}C NMR Spectral Data of Compounds (**1**) and (**2**) [a]

	1				**2**	
	in CD_3COCD_3		in CD_3SOCD_3		in CD_3COCD_3	
No.	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1a		128.2		126.8		131.9
2a(6a)	7.15 (d, 8.4)	130.1	7.03 (d, 8.4)	129.3	7.19 (d, 8.4)	128.7
3a(5a)	6.74 (d, 8.4)	115.8	6.65 (d, 8.4)	115.2	6.78 (d, 8.4) [i]	115.5 [k, p]
4a (OH)		158.7	9.62 (br s)	158.2 [n]		157.8
7a	6.13 (d, 9.7)	88.5	5.99 (d, 9.5)	87.5	5.94 (d, 9.0)	89.0
8a	4.17 (d, 9.7)	51.4	3.87 (d, 9.5)	50.5	4.26 (d, 9.0)	49.3
9a		135.9		134.8		143.7
10a		122.6		120.9		120.4
11a (OH)		155.1	9.19 (br s)	154.3 [g]		156.6 [l]
12a	6.29 (d, 2.2)	102.0	6.14 (d, 2.1)	101.1	6.32 (d, 2.0)	100.9
13a (OH)		156.3	9.00 (br s)	155.43 [o]		156.6 [l]
14a	6.14 (d, 2.2) [b]	109.1	5.89 (br s)	107.9	6.35 (d, 2.0) [j]	104.7
1b		133.6		132.3 [h]		134.6
2b(6b)	7.48 (d, 8.4)	131.4	7.30 (d, 8.4)	130.3	7.16 (d, 8.4)	128.8
3b(5b)	6.82 (d, 8.4) [c]	115.6 [m]	6.73 (d, 8.4) [e]	115.0	6.75 (d, 8.4)	115.5 [k, p]
4b (OH)		155.9	9.43 (br s)	157.3		155.8
7b	5.28 (d, 3.5) [d]	37.8	5.07 (d, 4.8)	36.4	6.48 (s)	37.8
8b	3.35 (dt, 9.9, 3.5)	52.9	2.94 (m)	52.0		135.2
9b		155.3		154.3 [g]		143.2
10b (OH)	5.10 (br s)	72.7	6.05 (br s) [f]	71.3		114.5
11b		178.9		178.4		159.0
12b	5.28 (s) [d]	99.0	5.28 (s)	98.1	6.03 (s)	94.1
13b		185.8		185.3		153.2
14b		140.2		138.9		123.6
1c		132.3		130.7		127.3
2c(6c)	6.46 (d, 8.4)	128.6	6.26 (d, 8.4)	127.7	6.49 (d, 8.7)	130.1
3c(5c)	6.49 (d, 8.4)	115.7	6.40 (d, 8.4)	115.1	6.59 (d, 8.7)	115.4
4c (OH)		156.1	8.96 (br s)	155.46 [o]		156.6 [l]
7c	3.93 (t, 9.9)	55.0	3.71 (t, 9.8)	53.5		147.6
8c	4.32 (dd, 9.9, 3.5)	51.2	4.24 (dd, 9.8, 3.3)	48.7	5.16 (s)	51.6
9c		141.2		140.2		138.0
10c		123.3		122.2		123.4
11c		161.3		159.9		160.8
12c	6.14 (d, 2.0) [b]	95.5	6.08 (d, 1.5)	94.8	6.11 (d, 2.0)	95.3
13c (OH)		158.9	9.11 (br s)	158.1 [n]		158.5
14c	6.51 (br d, 2.0)	106.7	6.19 (br s)	105.6	5.94 (d, 2.0)	106.5
1d		133.9		132.3 [h]		134.3
2d(6d)	7.41 (d, 8.4)	129.0	7.27 (d, 8.4)	128.1	7.25 (d, 8.6)	127.8
3d(5d)	6.82 (d, 8.4) [c]	115.4 [m]	6.73 (d, 8.4) [e]	114.8	6.78 (d, 8.6) [i]	115.6 [p]
4d (OH)		157.9	9.31 (br s)	154.6		157.5
7d	5.17 (d, 5.3)	94.9	5.14 (d, 5.1)	93.7	5.58 (d, 5.1)	93.9
8d	4.84 (d, 5.3)	56.3	4.70 (d, 5.1)	55.8	5.17 (d, 5.1)	56.3
9d		147.9		146.7		148.0
10d(14d)	5.88 (br s)	106.7	5.81 (br s)	105.6	6.40 (br d, 2.0)	107.8
11d(13c) (OH)		159.2	8.95 (br s)	158.7		159.5
12d	6.19 (t, 2.0)	101.7	6.05 (t, 2.0) [f]	101.0	6.35 (t, 2.0) [j]	101.7
Ph-OH	7.91-8.36 (br s)				8.00, 8.26, 8.48, 8.55 (1H each, br s) 8.25, 8.30. 8.33 (2H each, br s)	

a : Measured at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR). b - l : Overlapping. m - p : Interchangeable.

h x 3), MeOH (8 L x 24 h x 3) and 70% MeOH (8 L x 24 h x 2) at rt. Concentrated extracts gave respective residues [135 g (acetone), 70 g (MeOH) and 32 g (70% MeOH)]. A part (11 g) of the acetone extract was subjected to chromatography on ODS eluted with a mixture of MeOH-H_2O (20% MeOH – 70% MeOH) to give 23 fractions. The 40% MeOH fraction (Fr. 9) was further divided into 20 subfractions (Frs. 9.1-9.20) by Sephadex LH 20 (MeOH). The eighth fraction (Fr. 9.8) was purified with preparative TLC [EtOAc-$CHCl_3$-MeOH-H_2O (15:8:4:1)] to afford **1** (15 mg). Compounds (**2**) (4 mg), (**3**) (120 mg), (**4**) (195 mg), (**5**) (12 mg) and (**6**) (10 mg) were obtained from the fractions Fr. 9.19, Fr. 9.15, Fr. 9.10, Fr. 9.6 and Fr. 9.4, respectively, after purification by preparative TLC [EtOAc-$CHCl_3$-MeOH-H_2O (15:8:4:1)].

Table 2 HMBC and NOESY Spectral Data of **1** and **2** [a]

	1		**2**	
No.	HMBC	NOESY	HMBC	NOESY [d]
2a(6a)	4a, 7a	7a, 8a, 14a	4a, 7a	7a, 8a, 14a
3a(5a)	1a, 4a		1a, 4a	
7a	2a(6a), 8a	2a(6a), 14a [b]	1a, 2a(6a), 8a, 9a	2a(6a), 14a
8a	1a, 7a, 9a, 10a, 14a, 9b, 10b	2a(6a), 2b(6b), 14a	1a, 7a, 9a, 10a, 14a, 1b, 9b, 10b	2a(6a), 2b(6b), 14a
12a	10a, 11a, 13a, 14a		10a, 11a, 13a, 14a	
14a	8a, 10a, 12a, 13a	2a(6a), 7a [b], 8a, OH-10b	8a, 10a, 12a, 13a	2a(6a), 7a, 8a
2b(6b)	4b, 7b	8a, 7b, 7c, 14c	4b, 7b	8a, 7b, 14c
3b(5b)	1b, 4b		1b, 4b	
7b	9a, 10a, 11a, 1b, 2b(6b), 8b, 9b	2b(6b), 2c(6c)	9a, 10a, 11a, 1b, 2b(6b), 8b, 9b	2b(6b)
8b	10a, 1b, 7b, 9b, 14b, 1c, 7c, 14c	2c(6c), 8c		
12b	10b, 11b, 14b		10b, 11b, 13b, 14b	
2c(6c)	4c, 7c	7b, 8b, 7c, 8c, 8d, 10d(14d)	4c, 7c	8c, 8d, 10d(14d), 14c
3c(5c)	1c, 4c		1c, 4c	
7c	7b, 8b, 1c, 2c(6c), 8c, 9c	2b(6b), 2c(6c), 14c		
8c	9b, 14b, 1c, 7c, 9c, 10c, 14c	8b, 2c(6c), 8d, 10d(14d)	9b, 13b, 14b, 7c, 9c, 10c, 14c	2c(6c), 10d(14d), 14c
12c	10c, 11c, 13c, 14c		10c, 11c, 13c, 14c	
14c	8c, 10c, 12c, 13c	2b(6b), 7c	8c, 10c, 12c, 13c	2b(6b), 2c(6c), 8c
2d(6d)	4d, 7d	7d, 8d, 10d(14d) [c]	4d, 7d	7d, 8d
3d(5d)	1d, 4d		1d, 4d	
7d	11c, 1d, 2d(6d), 8d, 9d	2d(6d), 10d(14d)	10c, 11c, 1d, 2d(6d), 8d, 9d	2d(6d), 10d(14d)
8d	9c, 10c, 11c, 1d, 7d, 9d, 10d(14d)	2c(6c), 8c, 2d(6d), 10d(14d)	9c, 10c, 11c, 1d, 7d, 9d, 10d(14d)	2c(6c), 2d(6d), 10d(14d)
10d(14d)	8d, 11d(13d), 12d	2c(6c), 8c, 2d(6d) [c], 7d, 8d	8d, 11d(13d), 12d	2c(6c), 8c, 7d, 8d
12d	10d(14d), 11d(13d)		10d(14d), 11d(13d)	
OH-10b		14a, [b] 8b [b]		

a : Measured in CD_3COCD_3. b : Observed clearly in CD_3SOCD_3. c : Weak correlations.
d : NOEs for H-2c(6c)/H-7b and H-8c/H-8d cannot be found due to their vicinity of chemical shifts.

Upunaphenol F (1) : A pale yellow amorphous powder. $[\alpha]_D^{25}$ +5.6° (*c*= 0.1, MeOH); UV λ_{max} (MeOH) (nm (log ε)): 310 (sh, 3.64), 280 (4.23), 225 (sh, 4.79), 213 (4.86); IR ν_{max} (KBr) 3259, 1665, 1613, 1595, 1514, 1449; Negative ion HR–FAB–MS: $[M–H]^-$ *m/z* 921.2564 (Calcd 921.2547 for $C_{56}H_{41}O_{13}$); Negative ion FAB–MS: $[M–H]^-$ *m/z* 921; The ^1H and ^{13}C NMR spectral data are listed in Table 1.

Upunaphenol G (2) : A yellow amorphous powder. $[\alpha]_D^{25}$ –62.1° (*c*= 0.1, MeOH); UV λ_{max} (MeOH) (nm (log ε)): 310 (4.16), 293 (sh, 4.26), 285 (4.29), 225 (sh, 4.81), 215 (4.86); IR ν_{max} (KBr) 3348, 1612, 1512, 1449; Negative ion HR–FAB–MS: $[M–H]^-$ *m/z* 903.2449 (Calcd 903.2442 for $C_{56}H_{39}O_{12}$); Negative ion FAB–MS: $[M–H]^-$ *m/z* 903; The ^1H and ^{13}C NMR spectral data are listed in Table 1.

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