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A new resveratrol octamer, vateriaphenol A, in *Vateria indica*

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Abstract—A novel resveratrol octamer, vateriaphenol A, was isolated from stem bark of *Vateria indica* (Dipterocarpaceae). The structure and the relative configuration were confirmed on the basis of 1D and 2D NMR spectral data. Vateriaphenol A showed cytotoxicity against KB cells. © 2001 Elsevier Science Ltd. All rights reserved.

In our previous papers, we have studied stilbenoid oligomers in Dipterocarpaceous plants, the structures of stilbenoid derivatives in *Vatica*,[1–3] *Hopea*[4] and *Shorea* [5–7] and the cytotoxicity of some derivatives were discussed.[8] Among the isolates, the highest condensed oligomer was a resveratrol hexamer (vaticanol D[2]) isolated from stem bark of *Vatica rassak*. As part of an ongoing search for much higher condensed stilbenoid, an acetone extract of *Vateria indica* was further examined and a resveratrol octamer, vateriaphenol A (**1**), was isolated along with vatdiospyroidol[9] (vaticanol C[1]) (**2**) and (−)-hopeaphenol[4,5] (**3**). In this paper, the structure elucidation of vateriaphenol A is discussed.

An acetone extract (185 g) of the dried and ground bark (1.7 kg) of *V. indica* was subjected to column chromatography on silica gel ($CHCl_3$–MeOH gradient system) to give 18 fractions. Further purification of the 17th fraction [$CHCl_3$–MeOH (5:1)] by Sephadex LH-20 column chromatography (MeOH), preparative TLC (EtOAc–$CHCl_3$–MeOH–H_2O = 20:10:11:5) and reversed-phase medium-pressure column chromatography (H_2O–MeOH gradient system) achieved the isolation of **1** (96 mg). The other oligomers of **2** (60 mg) and **3** (19 g) were obtained from the 12th and 14th fractions [$CHCl_3$–MeOH (8:1)], respectively.

Vateriaphenol A (**1**), $[\alpha]_D^{25}$ −210 (MeOH) obtained as a brown amorphous powder showed a $[M+H]^+$ ion at m/z 1813 in the positive ion FABMS attributable to the empirical formula $C_{112}H_{84}O_{24}$, which is corresponding to a resveratrol (3,5,4′-trihydroxystilbene) octamer. The absorption bands in the UV spectrum were observed at 225 and 284 nm. The ^1H and ^{13}C NMR spectral data (measured at room temperature, as shown in Table 1) and ^1H, ^1H COSY (Fig. 1) indicated the presence of 16 aromatic rings which form a 4-hydroxyphenyl group (rings A_1-H_1), a 3,5-dihydroxy-1,2-disubstituted benzene (rings A_2, B_2, D_2 and G_2), a 3,5-dihydroxy-1,2,4-pentasubstituted benzene ring (ring C_2), a 3,5-dihydroxy-1,2,6-pentasubstituted benzene ring (ring E_2) and two 3,5-dihydroxy benzene ring (rings F_2 and H_2). Among the aromatics, the signals attributed to ring E_1 were observed as four broad singlets in the ^1H NMR spectrum [δ_H 6.40 (H-2e), 5.65 (H-3e), 6.40 (H-5e) and 7.30 (H-6e)], both of which came to split in proportion to low temperature, and become double doublets at −20°C.[10] These results were the same as a 4-hydroxyphenyl group in amurensins D–F.[11] The spectrum also exhibited four sets of mutually coupled aliphatic protons (H-7a/H-8a, H-7d/H-8d, H-7f/H-8f and H-7h/H-8h) and two sequence of four aliphatic protons in this order (H-7b/H-8b/H-8c/H-7c and H-7e/H-8e/H-7g/H-8g) as drawn by the bold line in Fig. 1. Considering the molecular formula, 24 aromatic oxygen functions were allotted for 20 hydroxyl groups and four ether linkages. The connection of eight resveratrol units was proposed by significant correlations observed via ^3J such as H-7a/C-2a(6a), H-8a/C-14a, H-7b/C-2b(6b), H-8b/C-10b, H-7c/C-2c(6c), H-8c/C-14c, H-7d/C-2d(6d), H-8d/C-14d, H-7e/C-1e, H-8e/C-1e, H-8e/C-10e, H-7f/

Keywords: natural product; resveratrol; octamer; cytotoxicity.
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Table 1. ^{1}H and ^{13}C NMR spectral data of vateriaphenol A (**1**)

No.	δ_H	δ_C		δ_H	δ_C
1a		131.55	1e		137.42
2a, 6a	7.21 (d, 8.8)	130.24	2e	6.40 (br s)[e]	131.27[k]
3a, 5a	6.79 (d, 8.8)	115.82[g]	3e	5.65 (br s)	115.82[g,k]
4a		158.19	4e		155.85
7a	6.13 (d, 11.7)	87.76	5e	6.40 (br s)[e]	116.95[k]
8a	4.13 (d, 11.7)[a]	49.20	6e	7.30 (br s)	130.46[k]
9a		143.12	7e	4.52 (d, 12.0)	50.70
10a		121.15	8e	4.13 (d, 12.0)[a]	56.50
11a		158.24	9e		148.15
12a	6.46 (d, 2.3)	101.09	10e		117.88
13a		157.35[h]	11e		162.08
14a	6.31 (br)	106.46	12e	6.26 (s)[f]	95.60
			13e		155.68
			14e		126.60
1b		135.35[i]	1f		134.75
2b, 6b	6.93 (d, 8.8)	129.25	2f, 6f	6.85 (d, 8.8)[d]	127.15
3b, 5b	6.55 (d, 8.8)[b]	115.14	3f, 5f	6.76 (d, 8.8)	115.68[j]
4b		155.59	4f		157.35[h]
7b	5.51 (br)[c]	41.89	7f	4.89 (d, 2.5)	92.90
8b	4.08 (br t, 2.3)	47.87	8f	2.05 (d, 2.5)	55.64
9b		139.45	9f		148.27
10b		118.91	10f, 14f	5.82 (d, 2.4)	107.08
11b		159.37	11f, 13f		159.19
12b	5.38 (d, 2.2)	95.30	12f	6.24 (t, 2.4)	101.47
13b		155.91			
14b	4.93 (d, 2.2)	110.73			
1c		135.19	1g		141.78
2c, 6c	6.85 (d, 8.8)[d]	128.95	2g, 6g	6.48 (d, 8.8)	127.82
3c, 5c	6.40 (d, 8.8)[e]	115.11	3g, 5g	6.40 (d, 8.8)[e]	115.68[j]
4c		155.47	4g		154.95
7c	5.51 (br)[c]	41.86	7g	3.20 (s)	56.74
8c	4.01 (br t, 2.3)	47.46	8g	3.65 (s)	55.57
9c		137.23	9g		144.37
10c		122.31	10g		120.85
11c		156.20	11g		161.32
12c		115.98	12g	6.26 (d, 1.8)[f]	94.96
13c		151.14	13g		159.32
14c	5.04 (s)	114.66	14g	6.55 (br s)[b]	109.14
1d		130.74	1h		135.35[i]
2d, 6d	6.25 (d, 8.8)	129.51	2h, 6h	7.15 (d, 8.8)	128.30
3d, 5d	6.52 (d, 8.8)	115.42	3h. 5h	6.74 (d, 8.8)	115.82[g]
4d		157.20	4h		157.80
7d	5.11 (d, 12.6)	86.20	7h	5.18 (d, 4.3)	94.19
8d	3.92 (d, 12.6)	48.65	8h	4.97 (d, 4.3)	56.25
9d		142.99	9h		149.24
10d		121.26	10h, 14h	6.03 (d, 2.4)	106.96
11d		158.15	11h, 13h		158.98
12d	6.58 (d, 2.2)	101.41	12h	6.05 (t, 2.4)	101.65
13d		157.30	OH	7.35 (C-13g), 7.60 (C-13c),	
14d	5.93 (br)	107.19		8.26 (C-13e), 8.49 (C-11d),	
				6.11, 7.43-8.41 (br s)	

Measured in CD_3COCD_3. 500 MHz (^{1}H) and 125 MHz (^{13}C). [a–j]: overlapping [k]: broad signal.

C-2f(6f), H-8f/H-10f(14f), H-7g/C-2g(6g), H-8g/H-10g, H-7h/C-2h(6h) and H-8h/C-10h(14h) in the HMBC spectrum (Fig. 1). The correlations were further observed between H-8a/C-9b, H-7b/C-9a, H-7c/C-9d, H-8d/C-9c, H-7e/C-13c, H-8f/C-11e, H-8g/C-13e, H-8h/C-11g, which indicated the connections between C-8a/C-10b, C-7b/C-10a, C-7c/C-10d, C-8d/C-10c, C-7e/C-12c, C-8f/C-10e, C-8g/C-14e and C-8h/C-10g, respectively. The two ether linkages forming a dihydrofuran ring (C-7f-O-C-11e and C-7h-O-C-11g) were supported by the cross peaks (H-7f/C-11e and H-7h/C-11g). Although no long-range correlation between H-7a/C-11b and H-7d/C-11c was observed, the presence of two dihydrofuran rings [C-7a(7d)-C-8a(8d)-C-10b(10C)-C-11b(11c)-O] was deduced after considering the molecular formula. The planar structure of vateriaphenol A was then established as shown in Fig. 1.

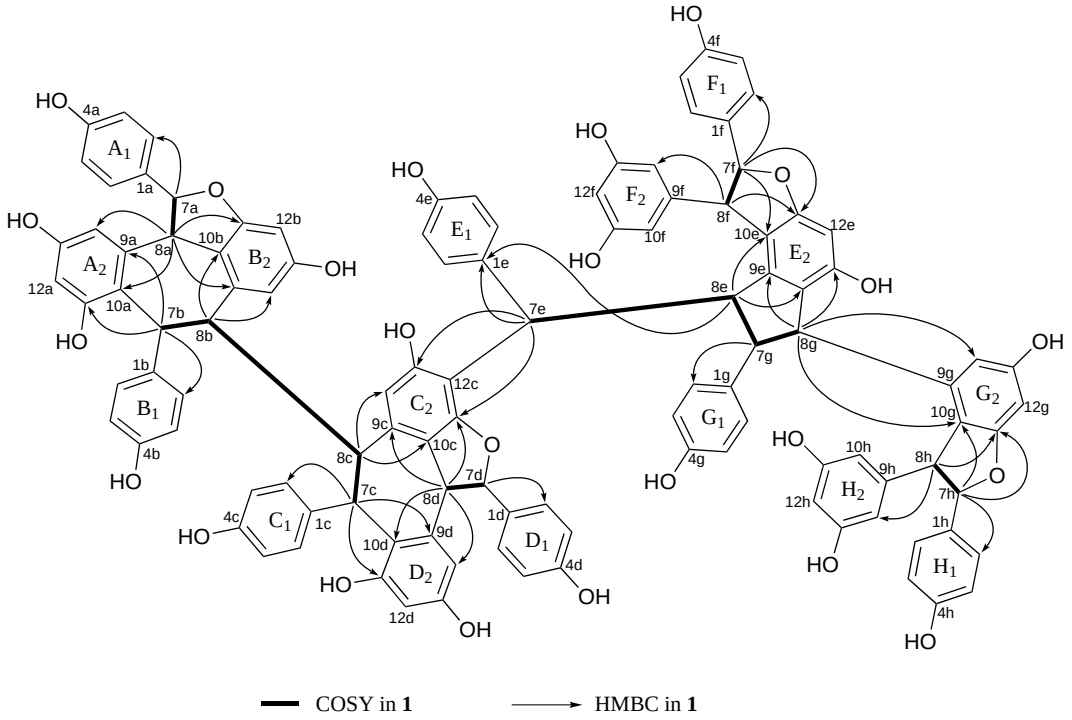

Figure 1. Planar structure and selected 2D NMR data of **1**.

The relative stereochemistry was determined by ROESY spectrum as shown in Fig. 2. The relative configuration is identical to those of hopeaphenol[4,5] (**3**) in one of tetrameric units (resveratrol A–D). In the other tetrameric unit (resveratrol E–H), the relative stereochemistry of five methine hydrogens (H-7f, H-8f, H-8e, H-7g and H-8g) is identical to those of vatdiospyroidol[9] (**2**) and the relationship between H-7e and H-8e is *trans* on the basis of *J* value (12.0 Hz).[12,13] The orientation of dihydrofuran ring was deduced to be *trans* from ROEs [H-7h/H-10h(14h) and H-8h/H-2h(6h)].

However, the presence of resveratrol oligomers ranging from dimer to hexamer has been hitherto reported,[2,14–16] the occurrence of an octamer condensed with resveratrols such as vateriaphenol A (1) is a first instance as natural product.

Vateriaphenol A showed the cytotoxicity against KB cells[17] with ED_{50} values at 10.5 μM.

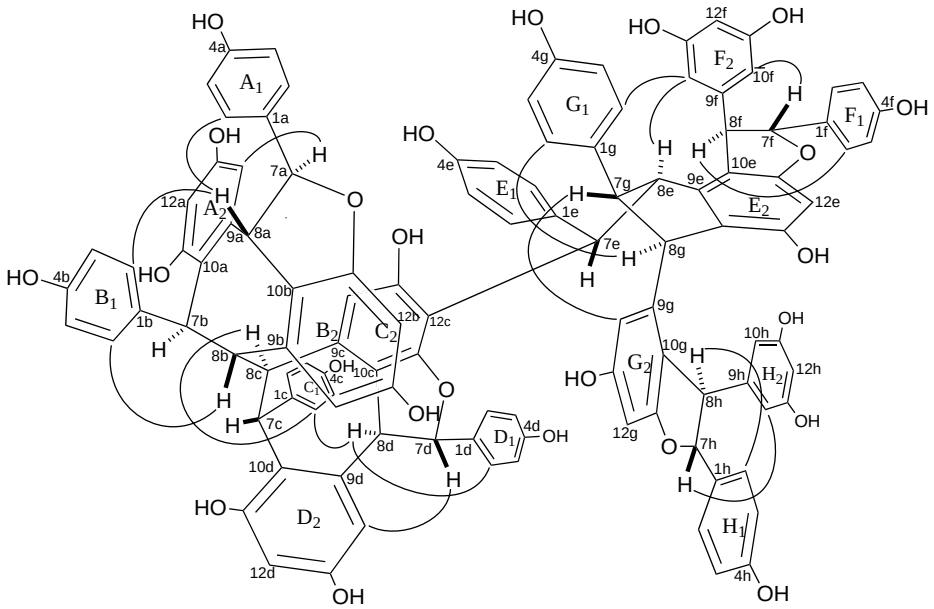

Figure 2. ROESY correlations in **1**.

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10. ^{1}H NMR (measured in CD_3COCD_3 at −20°C, signals attributed to ring E_1), δ_H: 6.30 and 7.32 (1H each, dd, $J=8.8$, 2.0 Hz, H-2e and 6e), 5.53 and 6.37 (1H each, dd, $J=8.8$, 2.2 Hz, H-3e and 5e).
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