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Rotational isomerism of a resveratrol tetramer, shoreaketone, in *Shorea uliginosa*

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Abstract—A new resveratrol tetramer, shoreaketone, was isolated from the stem bark of *Shorea uliginosa* (Dipterocarpaceae). The structure and the relative configuration were confirmed on the basis of 1D- and 2D-NMR spectral data. The structure has a novel framework of fused heptacyclic ring system including an α,β-unsaturated carbonyl group. In NMR spectra, shoreaketone is observed as two different conformers due to rotational isomerism.

Stilbene oligomers distributed widely in dipterocarpaceaeous plants[1–3] have been our topic of extensive structural investigation since the past five years. The tetramers of a resveratrol (3,5,4′-trihydroxystilbene) among them such as (−)-hopeaphenol,[4] vaticaphenol A[5] (vaticanol B[6]) and vatdiospyroidol[5] (vaticanol C[6]) occur widely and they are contained in high quantity in plants. They offer special interest because a large number of stereoisomers will be produced by a number of asymmetric carbons and the various frameworks when a resveratrol is homogeneously oligomerized. Their structural identification and NMR characterization still remains a difficult subject due to complicated stereochemistry that comprises diastereomer, epimer, and enantiomer,[7–9] but no example of rotational isomer in stilbene oligomers has been reported. As the wide-ranged bioactive screenings have been applied to stilbene oligomers and their significant activities have been revealed, exact structural identification is essential. Then we have been focusing on stereo structure of resveratrol oligomers.[6–12] In the present experiment, we found that a new resveratrol tetramer, shoreaketone (**1**), isolated from bark of *Shorea uliginosa* (Dipterocarpaceae) was different from the other resveratrol tetramers in respect to its skeleton and NMR spectral complexity. This letter refers to the isolation and structural elucidation of shoreaketone and its rotational isomerism.

An acetone extract (60 g) of the dried and ground bark (1.2 kg) of *S. uliginosa* was subjected to column chromatography on silica gel (EtOAc–$CHCl_3$–MeOH–H_2O gradient system) to give 57 fractions. Further purification of a combined fraction of the 8th–14th fractions [EtOAc–$CHCl_3$–MeOH–H_2O (160:80:11:2)] by repeated vacuum liquid chromatography [EtOAc–$CHCl_3$–MeOH–H_2O (80:40:11:2)] achieved the isolation of **1** (450 mg).

Shoreaketone (**1**), obtained as a yellow amorphous solid, showed a [M+Na]+ ion at *m/z* 929 in the positive-ion ESIMS attributable to the molecular formula $C_{56}H_{42}O_{12}$, which is corresponding to a resveratrol tetramer. Duplication of signals (in the ratio of 1:0.58) in the ^1H and ^{13}C NMR spectra (measured at room temperature (rt) in acetone-d_6 as shown in Tables 1 and 2)

Keywords: Rotational isomer; Resveratrol tetramer; Shoreaketone; *Shorea uliginosa*; Dipterocarpaceae.
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Table 1. ^{1}H NMR spectral data (600 MHz, CD_3COCD_3) of **1**

No.	**1a**	**1b**
2a, 6a	7.46 (d, 8.8)	7.44 (d, 8.8)
3a, 5a	6.86 (d, 8.8)	6.85 (d, 8.8)
7a	5.861 (d, 10.2)	5.864 (d, 10.2)
8a	5.149 (br d, 10.2)	5.152 (br d, 10.2)
12a	6.17 (d, 2.0)	6.07 (d, 2.0)
14a	6.46 (br s)	6.40 (br d, 2.0)
2b	4.75 (m)	3.81 (m)
3b	2.68 (dd, 17.0, 2.8)	2.35 (dd, 17.2, 2.8)
	3.08 (dd, 17.0, 1.6)	2.26 (dd, 17.2, 1.4)
5b	5.43 (d, 10.0)	5.29 (d, 10.0)
6b	6.39 (dd, 10.0, 2.2)	6.32 (dd, 10.0, 2.0)
7b	3.87 (d, 11.4)	3.78 (d, 11.4)
8b	3.67 (t, 11.4)	3.61 (t, 11.4)
12b	6.12 (d, 1.8)	6.14 (d, 1.8)
14b	6.09 (d, 1.8)	6.01 (d, 1.8)
2c	NI	NI
3c	NI	NI
5c	NI	NI
6c	NI	NI
7c	3.26 (d, 11.4)	3.18 (d, 11.4)
8c	3.59 (t, 11.4)	3.54 (t, 11.4)
12c	6.21 (d, 2.0)	6.30 (d, 2.0)
14c	6.76 (d, 2.0)	5.76 (d, 2.0)
2d, 6d	6.71 (s)	7.19 (d, 8.8)
3d, 5d	6.71 (s)	6.70 (d, 8.8)
7d	4.93 (d, 4.4)	5.21 (d, 2.0)
8d	3.30 (d, 4.4)	4.59 (d, 2.0)
10d	5.92 (d, 2.0)	5.96 (br s)
12d	6.05 (t, 2.0)	6.42 (t, 2.0)
14d	5.92 (d, 2.0)	6.46 (br s)
OH	8.35 (br s, C-13a)	8.29 (br s, C-13a)
	8.27 (br s, C-13b)	7.93 (br s, C-13b)
	8.36 (br s, C-13c)	8.27 (br s, C-13c)
	7.59 (br s, C-11d)	8.53 (br s, C-11d)
	7.59 (br s, C-13d)	8.58 (br s, C-13d)

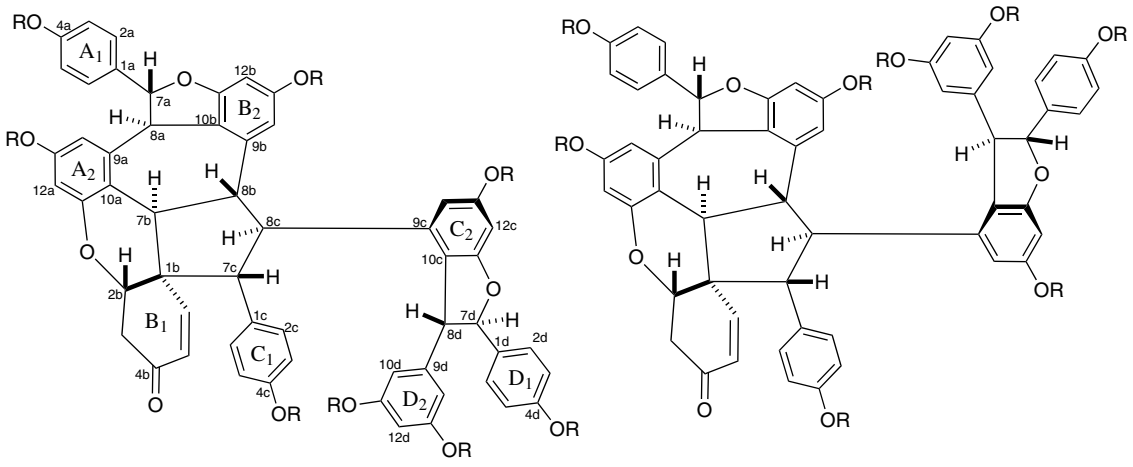
1a and **1b** represent major and minor conformers at 25 °C, respectively. NI: not identified.
Unassigned OH signals: 8.18, 8.21, 8.22, 8.31, 8.49, 8.49 (br s).

Table 2. ^{13}C NMR spectral data (150 MHz, CD_3COCD_3) of **1**

No.	**1a**	**1b**
1a	131.08	130.96
2a, 6a	129.07	128.93
3a, 5a	115.38(a)	115.38(a)
4a	157.73/157.65[a]	157.77/157.69[a]
7a	86.71(b)	86.71(b)
8a	49.76	49.85
9a	141.71	141.47
10a	113.28	113.00
11a	154.11	154.33
12a	101.01/100.93(c)[a]	101.01/100.93(c)[a]
13a	156.97/156.88[a]	156.79/156.70[a]
14a	105.14/105.06[a]	105.07/104.98[a]
1b	45.79	45.19
2b	75.30	75.02
3b	39.01(d)	39.01(d)
4b	195.03	195.22
5b	128.36	128.15
6b	153.13	153.64
7b	47.26	47.66
8b	49.05	46.81
9b	137.99	138.75
10b	117.25	116.94
11b	159.46	159.62
12b	96.44/96.36[a]	95.85/95.76[a]
13b (OH)	156.47/156.39[a]	157.89/157.72[a]
14b	109.00/108.91[a]	108.68/108.59[a]
1c	131.43	131.04
2c	NI	NI
3c	NI	NI
4c (OH)	156.44/156.39[a]	155.93/155.85[a]
5c	NI	NI
6c	NI	NI
7c	62.89	56.58
8c	56.53	62.02
9c	143.11	140.80
10c	119.80/119.70[a]	115.94/115.84[a]
11c	161.69	163.72
12c	95.41/95.32	95.76/95.67[a]
13c (OH)	159.35/159.24[a]	158.15/158.05[a]
14c	104.93/104.84[a]	112.81/112.70[a]
1d	132.45	133.59
2d, 6d	127.69	126.97
3d, 5d	115.18	115.30
4d (OH)	157.22/157.13[a]	157.27/157.20[a]
7d	93.54	93.42
8d	54.47	56.61
9d	145.85	148.26
10d	106.60/106.51[a]	105.72/105.63[a]
11d (OH)	158.34/158.24[a]	159.84/159.72(e)[a]
12d	101.42/101.34[a]	101.76/101.67[a]
13d (OH)	158.34/158.24[a]	159.84/159.72(e)[a]
14d	106.60/106.51[a]	106.51/106.42[a]

1a and **1b** represent major and minor conformers at 25 °C, respectively. NI: Not identified. (a–e): overlapping. Large signal is shown in each left side of slash.[17]
[a] Each signal was observed in duplicate in the intensity ratio 1:0.7–1:0.2.

suggested the existence of two conformers. The observed peaks were assignable to the structures of **1a** (major) and **1b** (minor) by means of 2D NMR spectroscopy at rt. The occurrence of rotational isomers of **1** was established by the following spectral properties. A band in the IR spectrum at 1660 cm^{-1} and a signal in the ^{13}C NMR spectrum (δ_C 195.03: **1a**; 195.22: **1b**) showed the presence of an α,β-unsaturated carbonyl group (C-4b). By usual methylation, **1** afforded an octamethyl ether [the structures of methyl ether of **1c** and **1d** are corresponding to those of **1a** and **1b** (the relative ratio observed in the ^{1}H NMR spectrum in acetone-d_6 is 1:0.25)],[13] which suggested that **1** had eight phenolic hydroxyl groups. In each case of **1a** and **1b**, the NMR spectrum (Tables 1 and 2) exhibited the presence of seven aromatic rings, which consisted of three 4-hydroxyphenyl groups (rings A_1, C_1, and D_1), three 3,5-dioxygenated-1,2-tetrasubstituted benzene rings (rings A_2–C_2) and a 3,5-dihydroxy benzene ring (ring D_2). Among the aromatic rings, any signals attributed to ring C_1 were not observed in the ^{1}H NMR spectrum measured at rt, they became to appear in low temperature and were observed as broad doublets at −20 °C.[14] These phenomena were similar to those of a 4-hydroxyphenyl group found in vateriaphenol A and vaticanol G, which can be explained by the fixed rotation of the ring caused by the steric hindrance due to neighboring substituent(s).[8,10] The spectrum also exhibited four sets of mutually coupled aliphatic protons (C*H*-7a/C*H*-8a, C*H*-2b/



1a : R = H
1c : R = CH_3

1b : R = H
1d : R = CH_3

Figure 1. Rotational heterogeneity in shoreaketone.

CH_2-3b,C*H*-7b/C*H*-8b/C*H*-7c/C*H*-8c and C*H*-7d/C*H*-8d) and a set of *cis*-olefinic protons (C*H*-5b/C*H*-6b) as drawn by the bold line in Figure 2. Existence of a partial structure of cyclohex-2-enone unit (C-1b–C-6b) was confirmed by the HMBC. Considering the molecular formula, three aromatic oxygen functions were allowed to be an ether linkage. By the aids of ^3J cross peaks in the HMBC spectrum (Fig. 2), these partial structures could be connected. Thus the planar structure of resveratrol tetramer, shoreaketone, was characterized as **1**.

According to NOESY experimental results, the relative stereochemistry of partial units, 1A and 1B in **1**, was retained in both **1a** and **1b**. The strong cross peak attributable to conformational exchange[15,16] was observed at H-14c of **1a** and H-14c of **1b** in the NOESY spectrum, indicating that **1** has two rotational isomers (**1a** and **1b)**. By the differential NOE spectrum the translated irradiation[15] of H-14c of **1a** enhanced H-14c of **1b**, and vice versa, which further supported the exchange. NOE correlations were observed between H-14c/H-7c and H-14c/H-8b in **1a** and H-14c/H-8c in **1b**, to the contrary, no correlations were done between H-14c/H-8c in **1a** and between H-14c/H-7c and H-14c/H-8b in **1b** (Fig. 3), which confirmed that the rotational isomerism was restricted by the C–C bond of C-8c/C-9c (Fig. 1). The relative ratio of **1a** and **1b** was varied by measured solvent and temperature, and it was 1:0.29, 1:0.37, and 1:0.42 by NMR measurement (in CD_3OD) at 50, 25, and −20 °C, respectively. The ^1H NMR spectrum at 85 °C in DMSO-d_6 still showed signals forming respective pairs as in acetone-d_6 and CD_3OD.

Our present structural characterization of shoreaketone (**1**) demonstrated the diversity of resveratrol oligomers

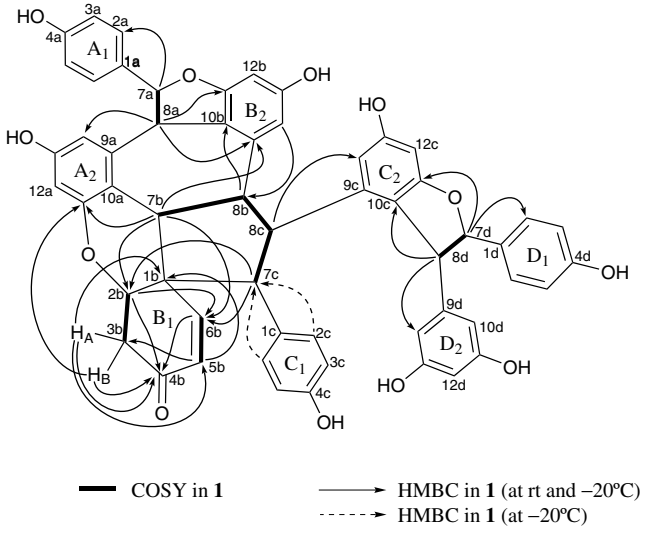


Figure 2. Planar structure and selected 2D NMR data of **1**.

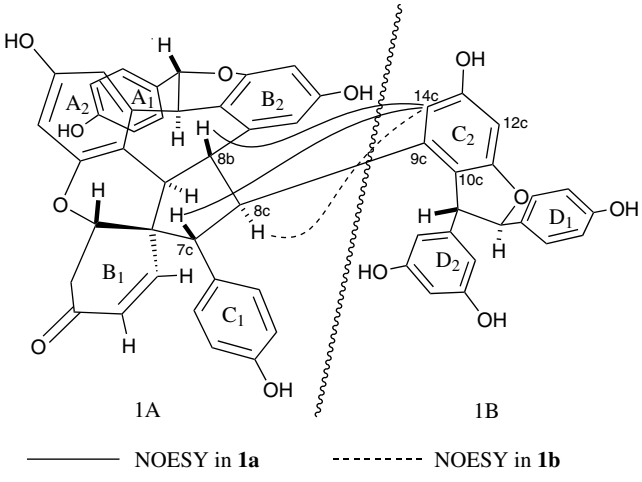


Figure 3. Key NOEs observed in the NOESY spectrum of **1**.

in dipterocarpaceaeous plants. The spectral properties and the detailed data will be fully discussed.

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13. Treatment of **1** (50 mg) with K_2CO_3 (2 g) and MeI (0.1 g) in dry acetone (20 mL) under reflux for 4 h provided permethylether in 96% yield. Negative ion HR-FABMS: *m/z* 1017.3842 for $C_{64}H_{57}O_{12}$ (observed) [M−H]-, calcd. 1017.3849.
14. ^{1}H NMR (measured in CD_3COCD_3 at −20 °C, signals attributed to ring C_1), δ H: 7.26 and 6.76 (1H each, br d, J = 8.3 Hz, H-2c and 6c of **1a**), 6.73 and 6.46 (1H each, br d, J = 8.3 Hz, H-3c and 5c of **1a**), 7.38 and 6.41 (1H each, br d, J = 8.3 Hz, H-2c and 6c of **1b**), 6.76 and 6.47 (1H each, br d, J = 8.3 Hz, H-3c and 5c of **1b**).
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