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Absolute structures of *C*-glucosides of resveratrol oligomers from *Shorea uliginosa*

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ABSTRACT

Two *C*-glucosides of resveratrol dimers (uliginoside A (**1**) and hemsleyanoloside B (**2**)) consisting of enantiomeric aglycones and two *C*-glucosides of resveratrol trimers (uliginosides B (**3**) and C (**4**)) consisting of diastereomeric aglycones were isolated from *Shorea uliginosa* (Dipterocarpaceae). These structures were elucidated by spectroscopic analysis including NMR experiments, and their absolute configurations were determined based on circular dichroism data. Resveratrol oligomers of *C*-glucosides with a 1,2-diaryldihydrobenzofuran ring are produced with specific biogenetic routes.

Many types of stilbenoid oligomers have been reported as constituents of a series of Dipterocarpaceaeous plants during this decade from our laboratory.[1a–e] In general, stilbene oligomers from this family are resveratrol oligomers, and their *O*- and *C*-glucosides. The various structures depend on the skeletal and stereochemical variations. A 1,2-diaryldihydrobenzofuran moiety in resveratrol oligomers may be biosynthesized by different stereochemical pathways depending on the plant family. Many stereochemical structures of the furan moiety are well characterized, and the stereochemical products from various plant families have been defined (e.g., Dipterocarpaceae, Gnetaceae, Cyperaceae, and Vitaceae).[1c] The absolute structure of the 1,2-diaryldihydrobenzofuran moiety in oligomers isolated from Dipterocarpaceae originates from (−)-ε-viniferin (resveratrol dimer), two chiral centers of which have been assigned as absolute *R* configurations.[2] (−)-ε-Viniferin plays a key role in the biosynthesis of oligomers in this family and the absolute stereochemistries of other oligomers (dimers, trimers, tetramers, etc.) were speculated based on its absolute structure.[3] The other enantiomer, (+)-ε-viniferin, has been isolated from Vitaceae, which also contributes to the stereo structures of other oligomers.[4] In the past decade, much interest in resveratrol[5a–c] and its oligomers[6a–c] have been shown due to their versatile bioactivities. As more structure-based drug design and screening are performed and clinical applications increase, a clear and accurate understanding of their absolute structure becomes necessary.

The genus *Shorea* (Dipterocarpaceae) is rich in *C*-glucosides of resveratrol oligomers.[1e] The major *C*-glucosides contain a 1,2-diaryldihydrobenzofuran moiety, which has biogenetic correlations with ε-viniferin. In the present study, absolute structures of enantiomeric aglycones of ε-viniferin (uliginoside A (**1**) and hemsleyanoloside B (**2**)) and di-*C*-glucosides of two diastereomeric resveratrol trimers, (uliginosides B (**3**) and C (**4**)), isolated from *Shorea uliginosa*, are described with a focus on the stereochemistry of two 1,2-diaryl-dihydrobenzofuran moieties. The absolute structure was determined based on the circular dichroism (CD) spectra of **1** and **2**. Application of the olefin cleavage strategy on the trimers to get CDs of the newly separated 2,3-diarylbenzofurans enabled assignments of their absolute stereochemistries.

Fractionation of the acetone extract of *S. uliginosa* ground bark and subsequent purification of polar fractions resulted in the isolation of four *C*-glucosides of resveratrol oligomers.[7] One of these is a known compound called hemsleyanoloside B (**2**).[1e] Structures of new compounds (uliginosides A (**1**), B (**3**), and C (**4**)) were established by the spectral evidence described below.

Uliginoside A (**1**), a dark green solid, showed a $[M-H]^-$ ion at *m/z* 777.2391 in the negative-ion FABMS attributable to the molecular formula $C_{40}H_{42}O_{16}$, which corresponds to a diglucoside of the resveratrol dimer. Analysis of ^1H and ^{13}C NMR spectral data (Tables 1 and 2), $^1H-^1H$, and $^{13}C-^1H$ COSY and HMBC spectral data revealed two resveratrol units (resveratrols A and B) consisting of two 4-hydroxyphenyl groups (rings A_1 and B_1), a 3,5-dihydroxy benzene ring (ring A_2), a 3,5-dioxygenated-1,2,4-pentasubstituted benzene ring (ring B_2), a set of mutually coupled aliphatic protons

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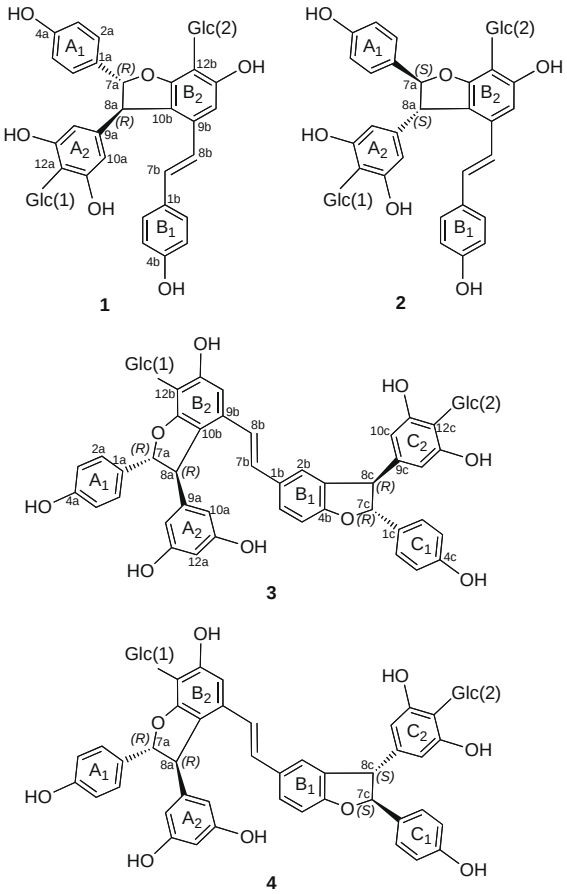


Table 1
^{1}H spectral data of **1**–**4**

No.		1	2[1e]	3	4
2a, **6a**		7.17 (d, 8.5)	7.24 (d, 8.5)	7.18 (d, 8.6)	7.13 (d, 8.3)
3a, **5a**		6.76 (d, 8.5)	6.75 (d, 8.5)	6.77 (d,8.6)	6.76 (d,8.3)
7a		5.40 (d, 5.6)	5.42 (d, 5.4)	5.40 (d, 6.8)	5.40 (d, 7.3)
8a		4.34 (d, 5.6)	4.31 (d, 5.4)	4.34 (d, 6.8)	4.30 (d, 7.3)
10a, **14a**		6.27 (s)	6.28 (br s)	6.17 (s)	6.13 (d, 2.0)
12a				6.17 (s)	6.10 (t, 2.0)
2b		7.07 (d, 8.5)	7.08 (d, 8.6)	6.84 (br s)	6.81 (br s)
3b		6.68 (d, 8.5)	6.67 (d, 8.6)		
5b		6.68 (d, 8.5)	6.67 (d,8.6)	6.73 (d, 8.3)	6.73 (d,8.3)
6b		7.07 (d, 8.5)	7.08 (d, 8.6)	7.04 (br d, 8.3)	7.05 (br d, 8.3)
7b		6.84 (d, 14.9)	6.83 (d, 14.9)	6.78 (d, 16.3)	6.81 (d, 16.3)
8b		6.57 (d, 14.9)	6.56 (d, 14.9)	6.53 (d, 16.3)	6.52 (d, 16.3)
14b		6.69 (s)	6.68 (s)	6.65 (br s)	6.66 (s)
2c, **6c**				7.12 (d, 8.6)	7.16 (d, 8.3)
3c, **5c**				6.76 (d, 8.6)	6.76 (d, 8.3)
7c				5.34 (d, 8.2)	5.28 (d, 8.3)
8c				4.30 (d, 8.2)	4.32 (d, 8.3)
10c, **14c**				6.17 (s)	6.13 (s)
Glucose-1	(−1)	4.90 (d, 9.8)	4.79 (d, 9.8)	4.80 (d, 9.9)	4.78 (d, 9.9)
	(−2)	3.95 (m)	4.15 (m)	4.14 (m)	4.13 (m)
	(−3)	3.48 (m)	3.48 (m)	3.48 (m)	3.46 (m)
	(−4)	3.48 (m)	3.39–3.48 (m)	3.50 (m)	3.50 (m)
	(−5)	3.39 (m)	3.39–3.48 (m)	3.40 (m)	3.41 (m)
	(−6)	3.77, 3.85 (m)	3.93–3.72 (m)	3.77–3.85 (m)	3.75–3.89 (m)
Glucose-2	(−1)	4.80 (d, 9.8)	4.91 (d, 9.8)	4.90 (d, 9.9)	4.94 (d, 9.9)
	(−2)	4.13 (m)	3.93 (m)	3.99 (m)	4.05 (m)
	(−3)	3.48 (m)	3.45 (m)	3.50 (m)	3.50 (m)
	(−4)	3.50 (m)	3.39–3.48 (m)	3.52 (m)	3.44 (m)
	(−5)	3.43 (m)	3.39–3.48 (m)	3.40 (m)	3.41 (m)
	(−6)	3.76,3.87 (m)	3.93–3.72 (m)	3.70–3.81 (m)	3.75–3.89 (m)

Measured in CD, OD. 300 MHz.

Table 2
^{13}C NMR spectral data of **1**–**4**

No.		1	2	3	4
la		134.0	134.3	133.7	133.6
2a, **6a**		128.1	127.9	128.3	128.7
3a, **5a**		116.4	116.2	116.27[a]	116.3[n]
4a		158.41[a]	158.2	158.3[c]	158.7
7a		94.7	94.3	94.8	94.9
8a		57.8	58.2	58.1[l]	58.5
9a		146.9	147.1	147.1	146.8
10a, **14a**		108.2	108.2	107.5	107.6[m]
11a, **13a**		158.6	158.7	159.7	159.8
12a		111.1	111.1	102.2	102.5
lb		130.2	130.2	131.9[r]	132.0[j]
2b		128.9	128.9	124.7	124.0
3b		116.5	116.5	132.1[r]	132.2[j]
4b		158.43[a]	158.5	160.8	161.3
5b		116.5	116.5	110.4	110.2
6b		128.9	128.9	128.1	129.0
7b		130.6	130.6	130.4	130.3
8b		123.3	123.3	123.8	123.9
9b		136.6	136.6	136.3	136.3
10b		120.2	120.1	120.4	120.7
l1b		161.3	161.4	161.2	161.0
12b		107.5	107.7	107.6	107.6[m]
13b		158.3	158.3	158.1	158.3
14b		104.9	105.2	104.8	104.8
lc				132.7	132.6
2c, **6c**				128.6	128.3
3c, **5c**				116.31[a]	116.3[n]
4c				158.5[c]	158.4[n]
7c				94.5	94.8
8c				58.1[l]	58.3
9c				144.8	144.7
10c, **14c**				108.5	108.5
11c, **13c**				158.3	158.4[n]
12c				111.2	111.1
Glucose-1	(−1)	76.6	76.8	76.4	76.5[o]
	(−2)	73.5	74.5	73.1	73.1
	(−3)	80.0	79.7	80.1	80.2
	(−4)	71.7[D]	71.3	71.6[g]	71.5
	(−5)	82.4	82.3	82.32[n]	82.4[p]
	(−6)	62.9[c]	62.1	62.7[i]	62.5[K]
Glucose-2	(−1)	76.5	77.5	76.5	76.5[o]
	(−2)	73.2	73.6	73.4	73.5
	(−3)	80.1	79.8	79.8	80.0
	(−4)	71.3[D]	71.1	71.3[g]	71.7
	(−5)	82.4	82.4	82.28[n]	82.4[p]
	(−6)	62.4[c]	62.4	62.4[i]	62.9[K]

Measured in CD, OD. 75 MHz. a–k : Interchangeable. 1–p: overlapping.

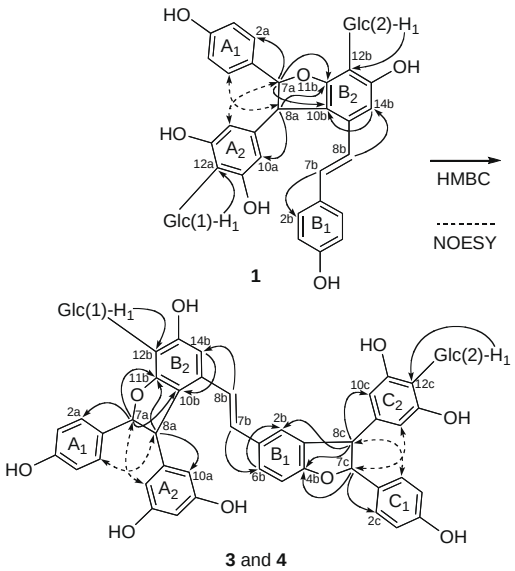


Figure 1. Selected 2D NMR Correlations for **1**, **3**, and **4**.

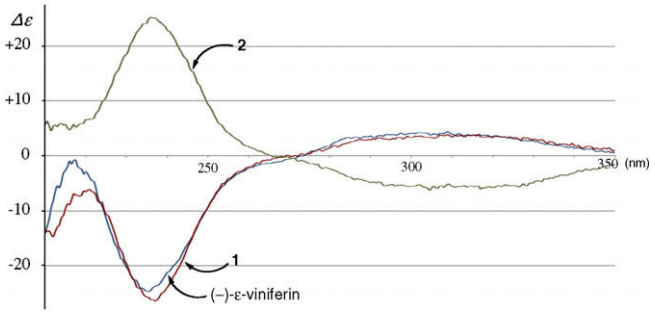
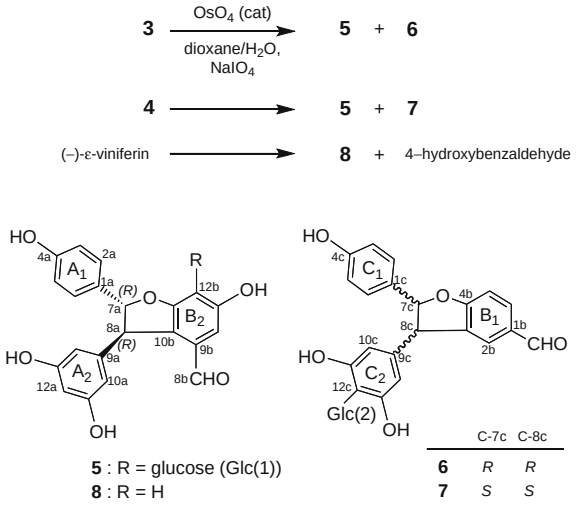


Figure 2. CD spectra of **1**, **2**, and (−)-ε-viniferin in MeOH.



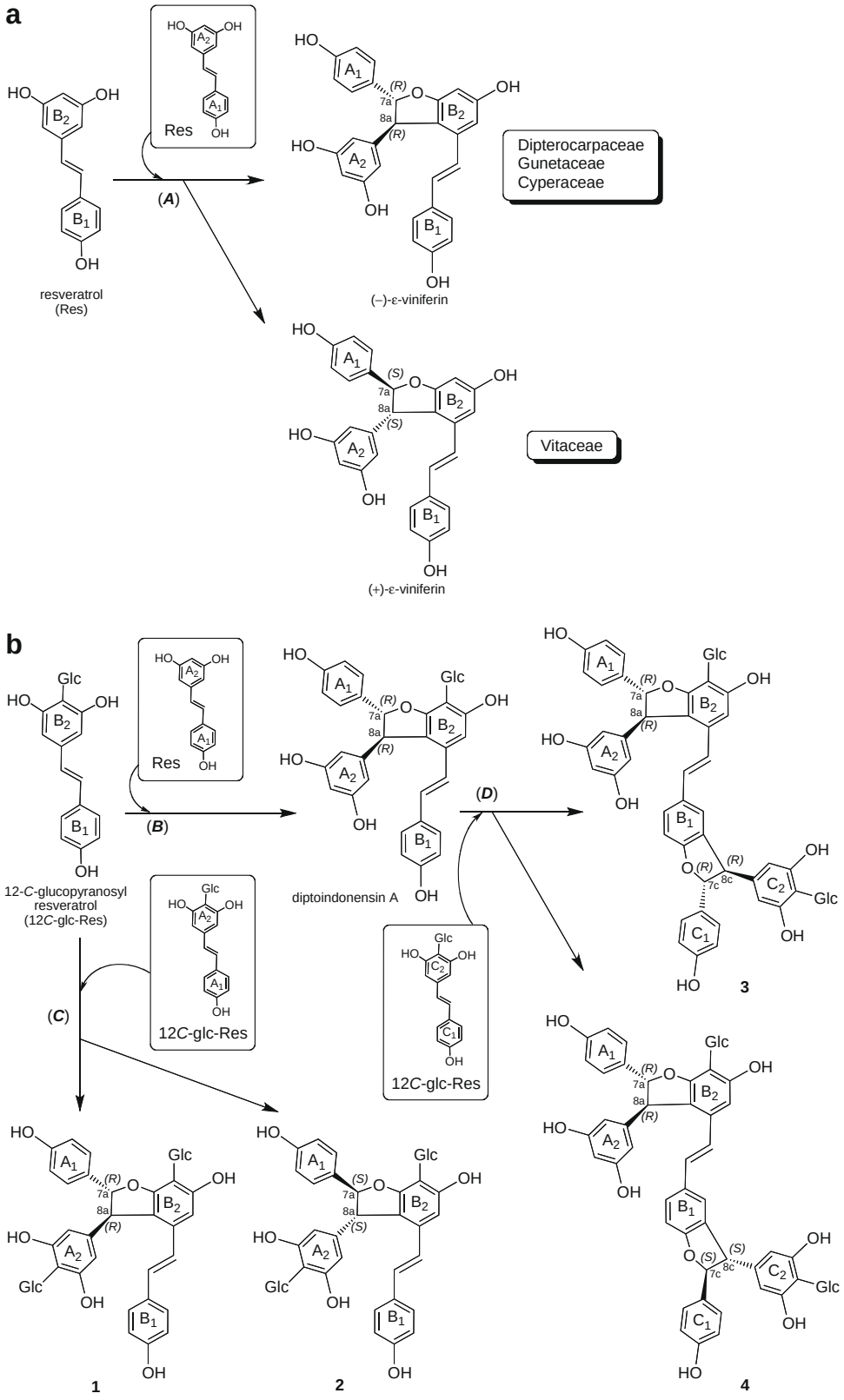
Scheme 1. Osmium tetroxide-catalyzed periodate oxidation of olefinic bond of **3**, **4**, and (−)-ε-viniferin.

(*CH*-7a/*CH*-8a), and a set of *trans*-olefinic protons (*CH*-7b/*CH*-8b). NMR spectral data also showed two *C*-glucopyranosyl moieties (Glc(1) and Glc(2)). The assignments ascribed to glucosyl parts of **1** substantiated the presence of a β-D-glucopyranosyl moiety as the common monosaccharide. Due to ^{3}J cross peaks in the HMBC spectrum (Fig. 1), these partial structures could be connected and the planar structure of **1** was characterized. *trans* Orientation of a 1,2-diaryl-dihydrobenzofuran moiety was elucidated by NOESY experiments. The aglycone was therefore determined to be ε-viniferin. The positions of glucose were confirmed to be at C-12a and C-12b by HMBC correlations.

The proposed relative stereochemistry of **1** is identical to the structure reported for **2** and their NMR spectral data resemble each other (Tables 1 and 2). The present configuration of **1** supported by the spectral evidence confirms the structure of **2**. For clarification, the absolute configuration was assigned based on the CD spectroscopic evidence. Lemiere et al. reported that the configurations at C-7 and C-8 of the dihydrobenzofuran skeleton can be distinguished from the region 220–240 nm.[8] Kurihara et al. reported the CD evidence of 7b,8b-dihydro-derivative of (−)-ε-viniferin [negative Cotton effect at 237 nm].[2] The CD spectra of **1** and **2** (Fig. 2) supported the conclusion that these compounds contain enantiomeric aglycones. Compound **1** exhibited the Cotton signal at 236 nm ($\Delta\varepsilon$ −26.6 (c = 20.2 μM, MeOH)); the sign and wavelength maxima are consistent with those of (−)-ε-viniferin[1d] (CD (c = 32.8 μM, MeOH) nm ($\Delta\varepsilon$): 236 (−24.8), H-7a: *R*; H-8a: *R*), suggesting that the aglycone of the proposed relative structure **1** has the same absolute configuration as (−)-ε-viniferin. The CD signals of **2** (CD (c = 20.6 μM, MeOH) nm ($\Delta\varepsilon$): 236 (+25.3)) supported the notion that the aglycone was (+)-ε-viniferin (H-7a: *S*; H-8a: *S*). The glucose stereogenicity of **1** and **2**, which is directly attached to the aryl rings in the *C*-β-D-glucosides, does not interfere with the exciton coupling that defines the furan stereogenic centers through exciton coupling observed at 236 nm.

Uliginosides B (**3**) and C (**4**) were obtained as brown solids. The respective compositions were deduced to be $C_{54}H_{52}O_{19}$ from the $[M+H]^+$ peaks at m/z 1005.3188 (for **3**, calcd 1005.3181) and 1005.3188 (for **4**, calcd 1005.3181) in the HR-FAB mass spectra. Three resveratrol units (resveratrols A–C) and two *C*-β-D-glucopyranosyl units (Glc(1) and Glc(2)) were supported by 1D and 2D NMR spectroscopic data (Fig. 1, and Tables 1 and 2). The respective NMR spectral similarities indicate that they possess stereoisomeric aglycones. The planar structures of **3** and **4** having two 1,2-diaryl-dihydrobenzofuran moieties were determined to be identical by HMBC spectral data (Fig. 1). All *trans* orientations of two 1,2-diaryldihydrobenzofuran rings were determined by NOESY experiments. The (*E*)-configuration of the C(7b)=C(8b) bond in **3** and **4** was inferred from ^{1}H NMR coupling constants (16.3 Hz). Their absolute configurations of chiral centers C(7a), C(8a), C(7c), and C(8c) could not be concluded by NMR spectral results. The stereochemical differences between **3** and **4** were attributed to the configurations of 1,2-diaryldihydrobenzofuran rings. To determine the absolute configurations of all quaternary carbon atoms in the 1,2-diaryldihydrobenzofuran rings, their CD spectra and oxidative products were analyzed. Both **3** and **4** were oxidized by the osmium tetroxide-catalyzed cleavage to give two aldehydes (**5** and **6** from **3**; **5** and **7** from **4**), respectively.[9] The ^{1}H NMR spectrum of each (**5**–**7**) exhibited an aldehyde proton as well as a *trans*-orientated 1,2-diaryl-dihydrobenzofuran moiety and a *C*-β-D-glucopyranosyl group (Table S1), which confirmed the structures **5**–**7**. (−)-ε-Viniferin was also treated in the same manner to give **8**.[9] The same CD spectral patterns were observed among **5**, **6**, and **8**, implying that they have identical stereochemistry. The spectrum of **7** showed a completely opposite pattern to **6**.[10] The absolute stereochemistry 7a*R*, 8a*R*, 7c*R*, and 8c*R* for **3** and 7a*R*, 8a*R*, 7c*S*, and 8c*S* for **4** was then established. The difference in the CD spectral patterns of mother compounds (**3**: (c = 19.9 μM, MeOH) nm ($\Delta\varepsilon$): 236 (−41.4), **4**: (c 19.9 μM, MeOH) nm ($\Delta\varepsilon$): 238 (−26.9)) is due to the stereochemistry of C-7c and C-8c. Compound **3** displays an almost two times enhanced negative Cotton effect to **1** at 236 nm, whereas **4** does not display clear enhancement. The absolute stereochemistries of the arylated stereogenic centers of two furan rings in a molecule are assignable based on comparison to the CD spectrum of ε-viniferin when both rings have identical stereochemistry (see Scheme 1).

ε-Viniferin has been isolated from Vitaceae, Dipterocarpaceae, Leguminosae, Cyperaceae, and Gnetaceae.[1c] Each family has a stereospecific biosynthetic pathway of oxidative condensation of two resveratrols that definitely produces one stable compound, (+)-ε-viniferin (Vitaceae) or (−)-ε-viniferin (Dipterocarpaceae and others). ε-Viniferin is also known as a biogenetically important precursor of many stilbene oligomers in Vitaceaeous and Dipterocarpaceaeous plants ((***A***): Scheme 2a)).[11] The aglycones of **1** and **2** are enantiomers, which correspond to (−)-ε-viniferin and (+)-ε-viniferin, respectively. The isolation of enantiomeric dimeric stilbene cores in the same original species is the first procedure. This finding clearly goes against the present concept that the Dipterocarpaceaeous plants produce enantiomers derived from the (−)-ε-viniferin building block.[1d] Diptoindonensin A[12] (mono-*C*-β-D-glucoside of (−)-ε-viniferin) is presumed to be produced by a condensation of resveratrol that would produce an aglycone of (−)-ε-viniferin ((***B***): Scheme 2b)), and is regarded as the major intermediate of **3** and **4** because they have the same absolute stereochemistry in the unit of (−)-ε-viniferin (resveratrols A and B). The stereochemical differences are due to the other 1,2-diaryldihydrobenzofuran units (ring B1—resveratrol C). These evidences suggest the existence of two pathways of formation of



Scheme 2. Proposed biogenetic pathways of *trans*-oriented 1,2-diaryldihydrobenzofuran rings. (a) (+)- and (−)-ε-viniferin formation in the plant species of Dipterocarpaceae, Gunetaceae, Cyperaceae, and Vitaceae Families; (b) biogenetic correlations of **1**–**4**.

trans-oriented 1,2-diaryldihydrobenzofuran rings in all cases, including a condensationof 12-*C*-β-D-glucopyranosyl resveratrols that can reasonably explain the coexistence of **1**–**4** ((***C***) and (***D***): Scheme 2b)). The HPLC-PDA analysis of the acetone extract of *S. uliginosa* does not show a peak due to ε-viniferin (data not shown) that would deny the coexistence of (+)- and (−)-forms of aglycones. Our present structural characterization of **1**–**4** not only adds a novel aspect of the biogenesis of stilbene oligomers but also dem-

onstrates additional diversity of resveratrol oligomers in Dipterocarpaceaeous plants.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.043.

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7. An acetone extract (60 g) of the dried and ground bark (1.2 kg) 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 42nd−45th fractions (EtOAc–$CHCl_3$–MeOH–H_2O (60:30:11:2)) by vacuum liquid chromatography (EtOAc–$CHCl_3$–MeOH–H_2O gradient system), Sephadex LH-20 column chromatography (eluted with MeOH), and ODS column chromatography (eluted with 40% MeOH), followed by HPLC separation (Shiseido CAPCELL PAK C18 UG120; eluted with 43% MeOH) isolated four compounds: **1** (320 mg), **2** (122 mg), **3** (148 mg), and **4** (82 mg).
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9. A mixture of water (1 ml), dioxane (3 ml), **3** (21 mg: 0.02 mmol), and osmium tetroxide (2.0 mg) was stirred for 5 min and maintained at 24–26 °C. During this process, sodium metaperiodate (10.7 mg, 0.05 mmol) was added over a period of 30 min. The tan colored slurry was then stirred for additional 1.5 h to give degradation products **5** (1.6 mg, a brown solid; $[\alpha]_D^{25}$ −41.0 (*c* 0.1, MeOH)) and **6** (4.5 mg, a pale yellow solid; $[\alpha]_D^{25}$ −68.4 (*c* 0.1, MeOH)), respectively. A similar reaction repeated with **4** (21 mg: 0.02 mmol) produced **5** (2.2 mg, a brown solid; $[\alpha]_D^{25}$ −36.8 (*c* 0.1, MeOH)) and **7** (6.4 mg, a pale yellow solid; $[\alpha]_D^{25}$ +66.0 (*c* 0.1, MeOH)). A same treatment of (−)-ε-viniferin (454 mg: 0.1 mmol) resulted in the isolation of degradation products **8** (160 mg, a pale yellow solid; $[\alpha]_D^{25}$ −142 (*c* 0.1, MeOH)) and 4-hydroxybenzaldehyde (49 mg).
10. All degradation products were characterized by their specific rotation,[9] CD, ^{1}H NMR (δ in ppm, acetone-d_6, 400 MHz) (Table S1), and FABMS spectral data. Compound **5**: CD (*c* 38.0 μM, MeOH) nm (Δε): 238 (−17.4); Positive ion FABMS *m/z*: 527 $[M+H]^+$. Compound **6**: CD nm (*c* 39.2 μM, MeOH) (Δε): 234 (−21.5), 272 (−6.4), 302 (+3.5); Positive ion FABMS *m/z*: 511 $[M+H]^+$. Compound **7**: CD (*c* 39.2 μM, MeOH) nm (Δε): 233 (+13.8), 272 (+5.0), 302 (−3.8); Positive ion FABMS *m/z*: 511 $[M+H]^+$. Compound **8**: CD (*c* 27.5 μM, MeOH) nm (Δε): 237 (−46.5); Positive ion FABMS *m/z*: 365 $[M+H]^+$.
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