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Absolute structure of shoreaketone: a rotational isomeric resveratrol tetramer in Dipterocarpaceaeous plants

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ABSTRACT

A rotational isomeric shoreaketone (**1**), identified as a skeletal member of resveratrol tetramers, was isolated from three species of Dipterocarpaceaeous plants: *Shorea uliginosa*, *Shorea hemsleyana*, and *Vateria indica*. The structure was elucidated by spectroscopic analysis including NMR experiments and their absolute configurations determined based on circular dichroism data. Shoreaketone has 10 asymmetric carbons and a framework of fused heptacyclic ring system including a spiro ring and an α,β-unsaturated carbonyl group that has not been reported in any other natural product. NMR experiments using shoreaketone indicate the presence of two conformers due to restricted rotation of a C–C bond in solution. The complex stereochemistry is due to its skeleton, 10 asymmetric carbons, and a chiral axis. The conformations of rotational isomeric stilbenoid were studied by variable-temperature NMR, ROESY, a skeletal conversion. The coexistence of two conformers for shoreaketone (**1**) was confirmed to be **1a** and **1b**, in which the diaryl-dihydrobenzofuran moiety (unit **1B**) is extended below or above the plane of the cyclopentane ring (unit **1A**), respectively.

1. Introduction

Several natural stilbenoids in Dipterocarpaceae and Vitaceae exist as 'oligomers' in which some stilbenoid molecules are coupled with others at various positions. These oligomeric stilbenoids have been shown to possess a wide range of physiological and biological properties, including anticancer,[1,2] anti-inflammatory,[3] and antiviral activities.[4,5] The oligomeric stilbenoids in Dipterocarpaceaeous plants have been our main focus of extensive structural investigation for the past decade.[6–14] The tetramers of a resveratrol (3,5,4′-trihydroxystilbene), such as (−)-hopeaphenol,[15] vaticanol B[6], and vaticanol C[6] are widespread and are present in large quantities in Dipterocarpaceaeous plants. These are of special interest due to the large number of stereoisomers resulting from many asymmetric carbons and the various frameworks obtained when a resveratrol is homogeneously oligomerized. About 120 stilbenoids of this type have been isolated from the Dipterocarpaceae family. Although a detailed structural determination based on NMR spectra is required as a part of ongoing chemical investigations, the difficulties caused by the complicated stereochemistry that comprise diastereomers, epimers, and enantiomers makes structural determination difficult. The complex stereostructure of stilbenoids causes hindered rotation of some benzene rings and adds to spectral complexity. Based on the stereostructures of epimeric and diastereomeric derivatives, CH–π and/or OH–π interaction has also been proposed.[8]

In the present study, the structural characterization of shoreaketone (**1**) isolated from three Dipterocarpaceaeous plants is described because **1** appears to be different from other resveratrol tetramers with respect to its skeleton and NMR spectral complexity.[11] The heterocyclic ring in **1** is unique and has not been recorded in any other natural product and contains a dense array of functionality and stereochemistry. Shoreaketone (**1**) is the first rotational isomeric stilbenoid with an arkyl–aryl axis. The isomerism is caused by a slow rotation about the axis due to steric hindrance. They therefore occur as two configurationally stable rotational isomers of **1a** and **1b**.

The NMR spectra of shoreaketone (**1**) exhibit multiplicity due to rotational isomerism at ambient temperatures (Supplementary data). Changes in the ratio of two conformers and in various solvents at the variable-temperature (VT) NMR and the cross peaks by a conformational exchange observed in NOESY experiments can be attributed to rotational isomerism. Complete and unequivocal

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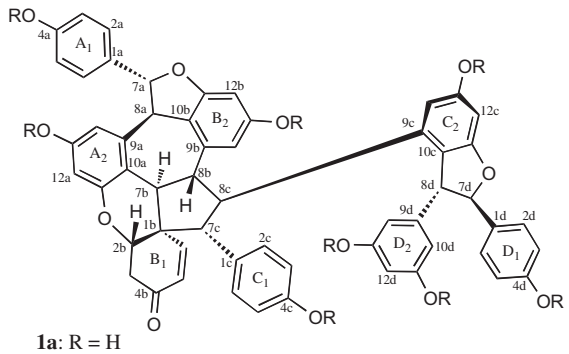
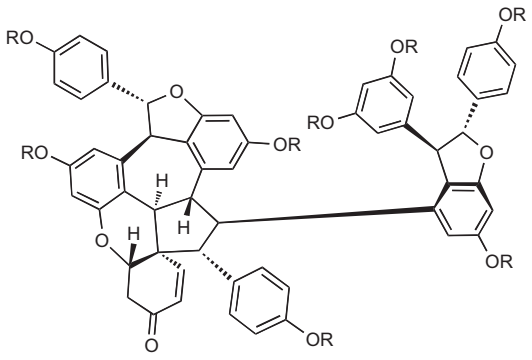
assignment of proton and carbon resonances of the two rotational isomers was demonstrated through structural analysis. The rotational state of rotamers could be defined using NOESY experiments that show the presence or absence of correlation between H-8c and H-14c. It was then possible to differentiate the two rotamers. The conformations are supported by the anisotropy that is explained by the different chemical shifts of H-2b and H-14c in the two rotamers.

An acid-catalyzed rearrangement of **1** resulted in formation of a mono alkyl ether of the known resveratrol tetramer, (+)-isohopeaphenol (**2**). It was found that **1** undergoes stereoselective rearrangement to form a monomethyl ether (**2a**) in excellent yield and high stereoselectivity when treated with methanolic trifluoromethane sulfonic acid or H_2SO_4. This skeletal transformation results in a stereodefined approach toward two heterocyclic ring systems in **1**. The work reported here is directed toward the isolation, structural elucidation, and rotational isomeric properties of shoreaketone (**1**).



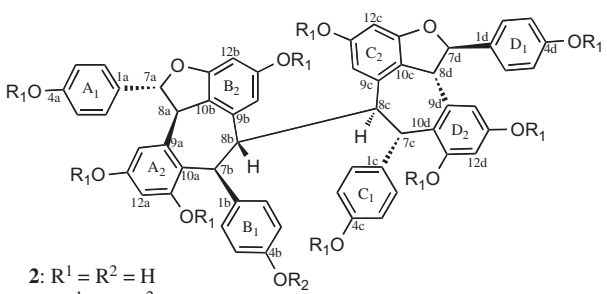
1a: R = H
1c: R = CH_3
1e: R = $COCH_3$

Extended Rotamer



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

Compact Rotamer



2: $R^1 = R^2 = H$
2a: $R^1 = H$, $R^2 = CH_3$
2b: $R^1 = H$, $R^2 = C_2H_5$
2c: $R^1 = R^2 = CH_3$

2. Results and discussion

2.1. Isolation

An acetone extract (60 g) of dried and ground bark (1.2 kg) of *Shorea uliginosa* was subjected to column chromatography on silica gel (EtOAc/$CHCl_3$/MeOH/H_2O gradient system) to provide 57 fractions. Further purification of combined fractions from the eighth to 14th fraction [EtOAc/$CHCl_3$/MeOH/H_2O (160:80:11:2)] by repeated vacuum liquid chromatography (VLC) [EtOAc/$CHCl_3$/MeOH/H_2O (80:40:11:2)] achieved the isolation of **1** (450 mg). Stem barks of *Shorea hemsleyana* and *Vateria indica* were similarly examined to isolate **1** (120 mg and 25 mg, respectively).

2.2. Planar structure of shoreaketone

Shoreaketone (**1**) is the first example of an atropisomeric stilbenoid isolated naturally. The structure and the brief spectral data, including the ^1H and ^{13}C NMR spectral data at rt have been mentioned in our previous communication.[11] The structure is composed of four resveratrol units (A–D; resveratrol A unit: i.e., between rings A_1 and A_2 via atoms C-7a and C-8a). A detailed elucidation was carried out as follows.

The molecular formula was established as $C_{56}H_{42}O_{12}$ from the HRESIMS data [*m*/*z* 929.2610 $[M+Na]^+$; 929.2574 calcd for $C_{56}H_{42}O_{12}Na$] together with the NMR spectral data, indicating 36° of unsaturation. The UV and IR spectra indicated the presence of aromatic rings [λ_{max} (log ε) 285 (4.14) nm; ν_{max} 1598 cm^{-1}]. The IR spectrum indicated the presence of an α,β-unsaturated carbonyl group (1743 cm^{-1}) and ether groups (1153 and 1173 cm^{-1}). Methylation of **1** yielded an octamethyl ether (HRESIMS: *m*/*z* 1041.3821 $[M+Na]^+$) and acetylation resulted in an octaacetate (HRESIMS : *m*/*z* 1265.3389 $[M+Na]^+$), respectively, suggesting that **1** bears eight phenolic hydroxyl groups. Considering the molecular formula, another four oxygen functions were allotted for a carbonyl group and three ether linkages. A formation of hydrazone further supports the existence of the carbonyl group.

In the ^1H NMR spectrum, signals due to an aromatic ring and hydroxyl groups became broadened and doubled at rt in acetone-d_6.[11] Duplication of signals in the ^1H and ^{13}C NMR spectra suggested the existence of two conformers. The relative proportions of the two forms in various conditions are listed in Table 1. Reducing the temperature resulted in some alterations in the spectral features and a varied ratio of **1a** and **1b**. When the spectrum was measured at rt in acetone-d_6 the ratio was 1 (**1a**):0.58 (**1b**), which changed to 1 (**1a**):0.74 (**1b**) at −20 °C. The ^1H NMR spectra measured in DMSO-d_6 showed a turnover ratio of **1a** and **1b** and temperature increase also showed alterations in the spectral features and the ratio of **1a** and **1b** (Fig. S1), indicating that solvent viscosity also controls the interconversion rate constants. This alteration strongly suggested that isomerization occurs in the solution depending on solvent (polarity and viscosity) and temperature. The methyl ether also displayed signal duplications in the ^1H NMR spectrum. The observed peaks are assignable to the structures of **1c** and **1d**. The conformers appeared as an equilibrium mixture in the ratio of 1 (**1c**):0.25 (**1d**). The acetate (**1e**) displayed no duplication of signals due to isomerism. The ^1H NMR spectrum of the deacetylated product was superimposed to that of **1**, which displayed signal duplications. The ^1H and ^{13}C NMR spectra of the hydrazone, which appeared as an equilibrium mixture of four conformers, were too complicated to assign.

As observed by Haslam et al. for the representative rotational isomeric compound catechin-(4a-8)-catechin,[16] the proton spectra of **1** predominantly showed one rotamer when the spectra were recorded in a high ratio of deuterium oxide (D_2O) in acetone-d_6. Supporting evidences of the rotational isomerism were obtained by

Table 1
Relative proportions of two conformers **1a** and **1b** under various solvent and temp conditions[a]

Solvent	Ratio (v/v)	Temp	1a	1b	
Acetone-d_6		−20	1.00	0.74	[b]
		25	1.00	0.58	[b]
		−60	1.00	0.58	[c]
		−40	1.00	0.60	[c]
		−20	1.00	0.72	[c]
		0	1.00	0.70	[c]
		10	1.00	0.68	[c]
		20	1.00	0.63	[c]
		30	1.00	0.58	[c]
		40	1.00	0.56	[c]
		50	1.00	0.50	[c]
DMSO-d_6		25	1.00	3.38	[b]
		40	1.00	2.98	[b]
		55	1.00	2.65	[b]
		70	1.00	2.49	[b]
		85	1.00	1.56	[b]
Methanol-d_4		−20	1.00	0.39	[b]
		0	1.00	0.39	[b]
		25	1.00	0.34	[b]
		50	1.00	0.23	[b]
Acetone-d_6-D_2O	10:0	25	1.00	0.58	[d]
	9:1	25	1.00	0.64	[d]
	4:1	25	1.00	0.65	[d]
	7:3	25	1.00	0.62	[d]
	3:2	25	1.00	0.57	[d]
	1:1	25	1.00	0.51	[d]
	2:3	25	1.00	0.35	[d]
	1:4	25	1.00	0.13	[d]

[a] The ratio of the two conformers was evaluated by the integral values of H-5b.
[b] 600 MHz.
[c] 300 MHz.
[d] 400 MHz.

altering the relative proportions of **1a** and **1b** in acetone-d_6 containing different portions of D_2O in acetone-d_6. Addition of small amounts of D_2O (up to 10%) resulted in a slight decrease in the population of **1a**. Further addition of D_2O resulted in a gradual incline in the proportion of **1a** with corresponding decrease in the signals due to **1b** (Table 1). When **1** was in 80% D_2O, **1a** occupied 87% of the population. These results reinforce the rotational isomerism of **1**.

Assignments of the ^1H and ^{13}C NMR spectra of **1a** and **1b** in acetone-d_6 are shown in a previous communication (measured at rt (Figs. S12 and S13))[11] and Tables 2 and 3 (measured at −20 °C (Figs. S5 and S6)). These assignments were developed primarily using ^1H–^1H COSY and ^1H–^{13}C HSQC as well as ^1H–^{13}C HMBC experiments (Fig. 1 and Table 4). The protocol used for assignment under different conditions was similar; hence only selected examples are described in detail here. In the ^1H NMR spectrum in acetone-d_6 at −20 °C, some aromatic and hydroxyl protons displayed sharpened signals. NMR data at −20 °C were applied to the following structural analysis. The major conformer in acetone (extended rotamer) (**1a**) was first analyzed to determine the structure of **1**. The primary discussion is based on first-order consideration.

The ^1H NMR spectrum shows two sets of *ortho* coupled aromatic signals from two *p*-hydroxyphenyl group (H-2a,6a/H-3a,5a and H-2d,6d/H-3d,5d: rings A_1 and D_1). The spectrum also showed eight signals for *meta* coupled aromatic protons due to four resorcinol-type aromatic rings (H-12a/H-14a, H-12b/H-14b, H-12c/H-14c, and H-10d,14d/H-12d: rings A_2–D_2) and four aliphatic methine sequence functionalities (H-7b/H-8b/H-8c/H-7c) were also observed in the spectrum. Benzylic proton signals characteristic of a diaryl-dihydrobenzofuran moiety were observed at δ_H 5.84 (H-7a)/5.170 (H-8a) and δ_H 4.90 (H-7d)/3.24 (H-8d) in the ^1H NMR spectrum of **1** and showed one-bond correlations with the ^{13}C NMR resonances at δ_C 87.59 (C-7a)/50.20 (C-8a) and δ_C 94.18

Table 2
^1H NMR spectral data at −20 °C (600 MHz, CD_3COCD_3) of **1**

No. (^1H)	1a	1b
H-2a,6a	7.49 (2H, d, 8.8)	7.46 (2H, d, 8.8)
H-3a,5a	6.85 (2H, d, 8.8)	6.85 (2H, d, 8.8)
H-7a	5.84 (1H, d, 10.4)	5.85 (1H, d, 10.4)
H-8a	5.170 (1H, br d, 10.4)	5.174 (1H, br d, 10.4)
H-12a	6.15 (1H, d, 2.0)	6.04 (1H, d, 2.0)
H-14a	6.44 (1H, br s)	6.38 (1H, br s)
H-2b	4.76 (1H, m)	3.85 (1H, m)
H-3b(α)	2.68 (1H, dd, 17.0, 3.0)	2.35 (1H, dd, 17.2, 3.4)
H-3b(β)	3.14 (1H, dd, 17.0, 1.2)	2.21 (1H, dd, 17.2, 1.4)
H-5b	5.44 (1H, d, 10.1)	5.30 (1H, d, 10.1)
H-6b	6.45 (1H, dd, 10.1, 2.2)	6.35 (1H, dd, 10.1, 2.2)
H-7b	3.92 (1H, d, 11.2)	3.83 (1H, d, 10.8)
H-8b	3.69 (1H, t, 11.2)	3.60 (1H, t, 10.8)
H-12b	6.10 (1H, d, 1.8)	6.12 (1H, d, 1.8)
H-14b	6.08 (1H, d, 1.8)	6.00 (1H, d, 1.8)
H-2c	7.26 (1H, br d, 8.3)	7.38 (1H, br d, 8.3)
H-3c	6.73 (1H, br d, 8.3)	6.76 (1H, br d, 8.3)
H-5c	6.46 (1H, br d, 8.3)	6.47 (1H, br d, 8.3)
H-6c	6.76 (1H, br d, 8.3)	6.41 (1H, br d, 8.3)
H-7c	3.26 (1H, d, 9.2)	3.15 (1H, d, 10.8)
H-8c	3.57 (1H, dd, 11.2, 9.2)	3.51 (1H, t, 10.8)
H-12c	6.19 (1H, d, 2.0)	6.30 (1H, d, 2.2)
H-14c	6.77 (1H, d, 2.0)	5.73 (1H, d, 2.2)
H-2d,6d	6.68 (2H, d, 8.8)	7.19 (2H, d, 8.8)
H-3d,5d	6.70 (2H, d, 8.8)	6.68 (2H, d, 8.8)
H-7d	4.90 (1H, d, 4.6)	5.20 (1H, d, 2.0)
H-8d	3.24 (1H, d, 4.6)	4.61 (1H, d, 2.0)
H-10d	5.90 (1H, d, 2.0)	5.90 (1H, br s)
H-12d	6.02 (1H, t, 2.0)	6.40 (1H, t, 2.0)
H-14d	5.90 (1H, d, 2.0)	6.51 (1H, br s)
OH	8.74 (1H, br s, OH-13a)	8.68 (1H, br s, OH-13a)
	8.79 (1H, br s, OH-13b)	8.36 (1H, br s, OH-13b)
	8.59 (1H, br s, OH-4d)	8.64 (1H, br s, OH-13c)
	7.95 (1H, br s, OH-11d)	8.82 (1H, br s, OH-11d)
	7.95 (1H, br s, OH-13d)	8.97 (1H, br s, OH-13d)

1a and **1b** represent major and minor conformers at −20 °C, respectively. Unassigned OH signals: 8.60, 8.60, 8.69, 8.72, 8.89, 8.90 (br s).

Table 3
^{13}C NMR spectral data at −20 °C (150 MHz, CD_3COCD_3) of **1**

No. (^{13}C)	1a	1b
C-1a	131.38	131.28
C-2a,6a	130.12	129.94
C-3a,5a	116.03[a]	116.03[a]
C-4a	158.43/158.32*	158.51/158.41*
C-7a	87.59	87.56
C-8a	50.20	50.29
C-9a	142.40	142.18
C-10a	113.93	113.61
C-11a	154.76	154.94
C-12a	101.55/101.46[b,*]	101.55/101.46[b]
C-13a	157.62/157.52*	157.45/157.35*
C-14a	105.83/105.74*	105.73/105.63*
C-1b	46.35	45.76
C-2b	75.95	75.63
C-3b	39.72	39.63
C-4b	196.19	196.24
C-5b	128.97	128.77
C-6b	154.21	154.67
C-7b	47.72	48.01
C-8b	49.42	47.29
C-9b	138.74	139.47
C-10b	117.82	117.56
C-11b	160.03	160.24
C-12b	97.05/96.95*	96.47/96.38*
C-13b	157.14/157.05*	158.52/158.42*
C-14b	109.60/109.49*	109.35/109.27*
C-1c	132.10	131.62
C-2c	130.8703	130.4315
C-3c	116.4479	116.2762
C-4c	157.05/156.96*	156.64

Table 3 (*continued*)

No. (^{13}C)	**1a**	**1b**
C-5c	115.4273	115.0839
C-6c	131.00	132.2725
C-7c	63.31	56.99
C-8c	57.39	62.65
C-9c	143.88	141.52
C-10c	120.28	116.51
C-11c	162.20	164.42
C-12c	96.01/95.93	96.32/96.24*
C-13c	160.06/159.95*	158.8/158.72*
C-14c	105.59/105.51*	113.36/113.25*
C-1d	133.01	134.20
C-2d,6d	128.64	127.72
C-3d,5d	115.82	115.95
C-4d	157.93/157.82*	158.05/157.94*
C-7d	94.18	93.99
C-8d	54.90	56.99
C-9d	146.67	148.99
C-10d	107.03/106.95[c,*]	106.21/106.12*
C-11d	159.09/158.99[d,*]	160.48/160.36*
C-12d	101.95/101.87*	102.23/102.13*
C-13d	159.09/158.99[d,*]	160.56/160.47*
C-14d	107.03/106.95[c,*]	107.08/106.99*

1a and **1b** represent major and minor conformers at −20 °C, respectively.
*Each signals was observed in duplicate in the intensity ratio 1:0.7–1:0.2. The values on the left side of the slash represent large signals.
[a–d] Overlapping.

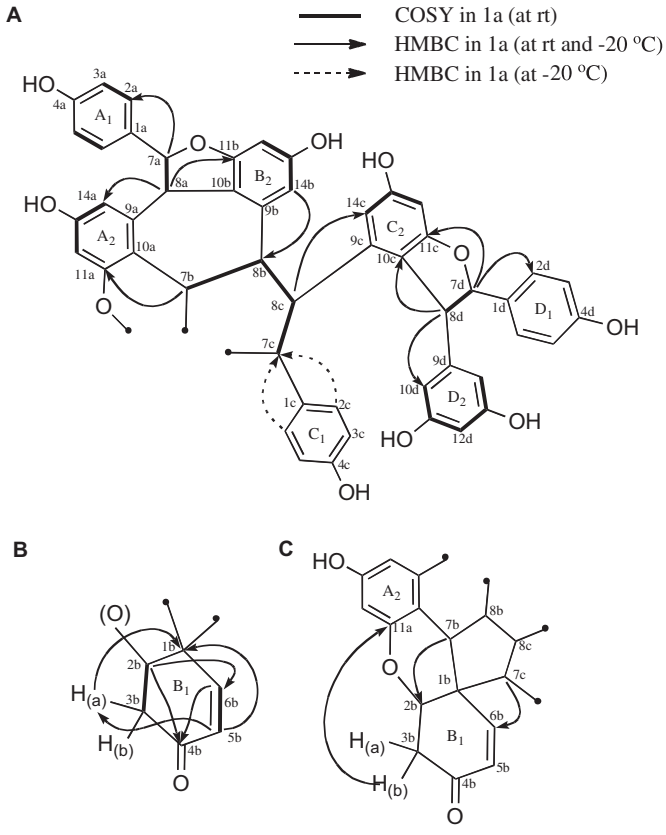


Fig. 1. Selected 2D-NMR correlations for the partial structures **A**–**C** of shoreaketone (**1**).

(C-7d)/54.90 (C-8d), respectively, in the ^{1}H–^{13}C HSQC spectrum, thereby indicating the presence of two diaryl-dihydrobenzofuran units in the molecule. In the ^{1}H NMR spectra of **1** measured under different conditions, complicated signal patterns were observed for H-2c, H-3c, H-5c, and H-6c due to different degrees of immobilization of ring C_1 by steric hindrance. At rt, the four H-atoms

Table 4
HMBC data of **1**[a]

No. (^{1}H)	No. (^{13}C)
H-2a	C-4a, C-6a, C-7a
H-3a	C-1a, C-4a, C-5a
H-5a	C-1a, C-3a, C-4a
H-6a	C-2a, C-4a, C-7a
H-7a	C-1a, C-2a, C-6a, C-8a, C-9a
H-8a	C-1a, C-7a, C-9a, C-10a, C-14a, C-9b, C-10b, C-11b
H-12a	C-10a, C-11a, C-13a, C-14a
H-14a	C-8a, C-10a, C-12a, C-13a
H-2b	C-4b, C-6b, C-7b, C-1c
H-3b(α)	C-1b, C-2b, C-4b, C-5b
H-3b(β)	C-4b, C-11a[d]
H-5b	C-1b, C-3b
H-6b	C-1b, C-2b, C-4b, C-7b
H-7b	C-9a, C-10a, C-11a, C-1b, C-2b, C-6b, C-8b, C-9b
H-8b	C-9a, C-7b, C-9b,[d] C-10b,[d] C-8c, C-9c
H-12b	C-10b, C-11b, C-13b, C-14b
H-14b	C-8b, C-10b, C-12b, C-13b
H-2c	C-1c, C-6c, C-4c, C-7c
H-3c	C-1c, C-4c, C-5c
H-5c	C-1c, C-3c, C-4c
H-6c	C-1c, C-2c, C-4c, C-7c
H-7c	C-1b, C-2b, C-6b, C-1c, C-8c, C-9c
H-8c	C-8b, C-9b, C-7c, C-9c, C-10c, C-14c
H-12c	C-10c, C-11c, C-13c, C-14c
H-14c	C-8c, C-10c, C-12c, C-13c
H-2d	C-4d, C-6d, C-7d
H-3d	C-1d, C-4d, C-5d
H-5d	C-1d, C-3d, C-4d
H-6d	C-2d, C-4d, C-7d
H-7d	C-10c,[e] C-11c, C-1d, C-2d, C-6d, C-8d, C-9d
H-8d	C-10c, C-1d, C-7d, C-9d, C-10d, C-14d
H-10d	C-7d, C-11d, C-12d, C-14d
H-12d	C-10d, C-11d, C-13d, C-14d
H-14d	C-7d, C-10d, C-12d, C-13d
OH-13a	C-12a, C-13a, C-14a
OH-13b	C-12b, C-13b, C-14b
OH-13c[b]	C-12c, C-13c, C-14c
OH-4d[c]	C-3d, C-4d, C-5d
OH-11d	C-10d, C-11d, C-12d
OH-13d	C-12d, C-13d, C-14d

[a] In acetone-d_6 at 600 MHz. Correlations were observed both at rt and −20 °C, and both in **1a** and **1b**, unless noted otherwise.
[b] Correlations for **1b**.
[c] Correlations for **1a**.
[d] Weak correlations.
[e] Not observed at −20 °C.

were scarcely observed because of extreme signal broadening in DMSO-d_6 and acetone-d_6. When the temperature was raised to 85 °C in DMSO-d_6, the equivalent protons of H-2c,6c (δ_H 6.90 (br s)) and H-3c,5c (δ_H 6.54 (br d)) appeared as two atom-integrated signals (Fig. S1). Under this condition, ring C_1 rotated almost freely. When the temperature was lowered in acetone-d_6, the four protons H-2c, H-6c, H-3c, and H-5c were observed as separated, broad signals at 0° (data not shown), and became a broad doublet at −20°. At such low temperatures, steric hindrance prevents ring C_1 from rotating freely, i.e., these protons are located in different chemical environments. Similar phenomena have been reported in some related stilbene oligomers of vaticanols G and H,[7] and vateriaphenol A.[10]

In the ^{1}H–^{13}C HMBC spectrum, significant correlations were observed between H-7a/C-2a,6a, H-8a/C-14a, H-8a/C-11b, H-7b/C-11a, H-14b/C-8b, H-8c/C-14c, H-7d/C-2d,6d, H-8d/C-10d,14d, and H-8d/C-10c, which support the connections between C-1a/C-7a, C-8a/C-9a, C-8a/C-10b, C-10a/C-7b, C-8b/C-9b, C-8c/C-9c, C-1d/C-7d, C-8d/C-9d, and C-10c/C-8d, respectively (Fig. 1, partial structure **A**). An additional cross peak observed for H-7d/C-11c supports the presence of an ether linkage, C-11c–*O*–C-7d, which is part of a dihydrobenzofuran moiety (C-7d–C-8d–C-10c–C-11c–*O*).

Although no long-range correlation with H-7a/C-11b was observed, the presence of another dihydrobenzofuran moiety (C-7a—C-8a—C-10b—C-11b—*O*) was deduced after considering the carbon chemical shift and the molecular skeleton. Based on the cross peaks observed for H-2c/C-7c and H-6c/C-7c in the $^{1}H-^{13}C$ HMBC spectrum at −20 °C (**A**), the position of ring C_1 was deduced to be C-7c. The remaining ring system and the connectivity in the molecule were determined as follows. Considering the molecular formula, the remaining unit in the molecule corresponds to C_6H_5O. The ^{1}H NMR spectrum also exhibited a set of mutually coupled aliphatic protons at δ_H 4.76 (H-2b), δ_H 2.68 (H-3b(α)), and δ_H 3.14 (H-3b(β)) and exhibited one-bond connectivities in the $^{1}H-^{13}C$ HSQC spectrum with the ^{13}C NMR signals at δ_C 75.95 (C-2b), δ_C 39.72 (C-3b), and δ_C 39.72 (C-3b), respectively. Another two signals in the ^{1}H NMR spectrum, at δ_H 5.44 (H-5b) and δ_H 6.45 (H-6b), which correlated with the ^{13}C NMR resonances at δ_C 128.97 (C-5b) and δ_C 154.21 (C-6b), respectively, were assigned for *cis*-olefinic protons. In the ^{13}C NMR spectrum, quaternary signals assigned to an aliphatic carbon at δ_C 46.35 (C-1b) and an α,β-unsaturated carbonyl carbon at δ_C 196.19 (C-4b) were also observed. These data suggested that the ring formed a cyclohex-2-enone ring (partial structure **B**: ring B_1), which was confirmed by the $^{1}H-^{13}C$ HMBC correlations between H-6b/C-4b, H-5b/C-3b(α), H-2b/C-4b, H-3b(α)/C-1b, and H-5b/C-1b. The important correlations of $^{1}H-^{13}C$ HMBC measurement for the fused cyclic system of ring B_1 were as follows; H-7b/C-2b, H-7c/C-6b, and H-3b(β)/C-11a (weak correlation: 4*J*) for the connection of C—C bonds and an ether linkage, C-1b/C-7b, C-1b/C-7c, and C-11a—*O*—C-2b in this order (partial structure **C**). Based on these results, the planar structure of **1** was confirmed.

2.3. Relative structure of shoreaketone

The stereostructure was determined from the results of the ROESY experiment [Fig. 2 (selected) and Table 5 (total)] and skeletal conversion. The trans orientations of H-7a/H-8a and H-7d/H-8d on the dihydrobenzofuran rings were confirmed by the distinctive ROEs between H-7a/H-14a, H-8a/H-2a,6a, H-14a/H-2a,6a, H-7d/H-10d,14d, H-2d,6d/H-10d,14d, and H-8d/H-2d,6d. The strong one (H-14a/H-2a,6a) and the large coupling constant (H-7a/H-8a: *J*=10.4 Hz) supported the trans diequatorial orientation of two aromatic rings (rings A_1 and A_2) and trans diaxial orientation of H-7a/H-8a,[1] namely, asymmetric carbon (C-8a) form the flap of the envelope conformation. Significant ROEs between H-14c/H-8b and H-14c/H-7c indicated that ring C_2, H-8b, and H-7c were of *syn* orientation on a cyclopentane ring (C-1b/C-7b/C-8b/C-8c/C-7c). The *syn* orientation of H-7b and ring C_1 was deduced based on the cross peaks observed for H-2c/C-7b in the spectrum at −20 °C. The large coupling constant values of H-7b/H-8b (*J*=11.2 Hz), H-8b/H-8c (*J*=11.2 Hz), and H-7c/H-8c (*J*=9.2 Hz) also supported the trans stereo relationship of four methine sequences, H-7b/H-8b/H-8c/H-7c. In addition, the *syn* orientation of the C—C bond (C-1b/C-6b), H-7b, and H-8a was supported by ROEs between H-7b/H-6b and H-7b/H-8a. Distinct ROEs of H-2b/H-7c and H-2b/H-8b indicated H-2b to be in β-orientation. Based on the results, the relative configuration of eight asymmetric carbons (C-7a, C-8a, C-1b, C-2b, C-7b, C-8b, C-7c, C-8c) in unit **1A** were determined as *rel-R*, *R*, *R*, *R*, *S*, *R*, *R*, *R*, respectively. The configurations of C-7d and C-8d in unit **1B** were determined as follows. A strong ROE was observed between H-14b/H-10d,14d, which indicated that the rings B_2 and D_2 were co-facial. Therefore, the orientation of C-7d and C-8d was determined to be *rel-R*. When the difference in the conformation of the cyclohex-2-enone ring (ring B_1) was considered, a boat and a chair conformation were indicated. It was found that the chair conformation of the ring system satisfied ROE (H-3b(β)/H-7c). The relative configuration and conformation of **1** were then established.

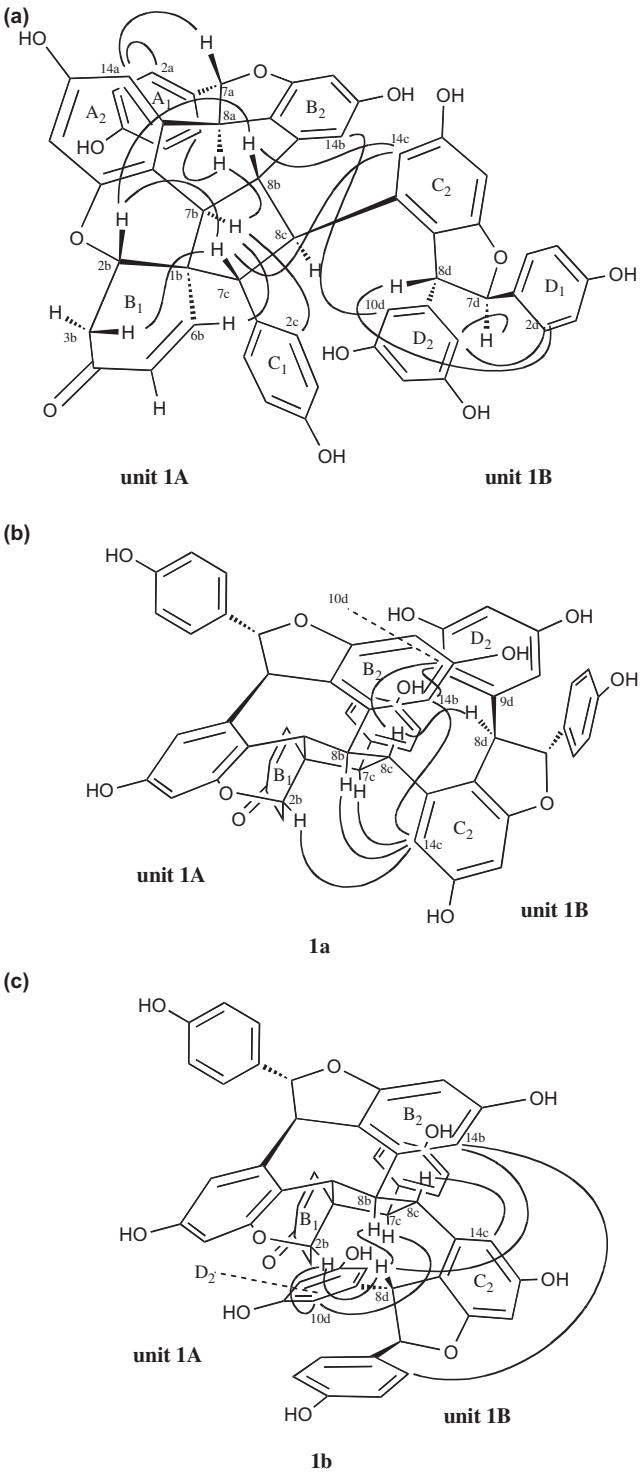


Fig. 2. Stereostructure and selected ROESY correlations (indicated by lines). ROEs observed for **1a** and **1b** (a), **1a** (b), and **1b** (c).

2.4. Skeletal conversion of shoreaketone

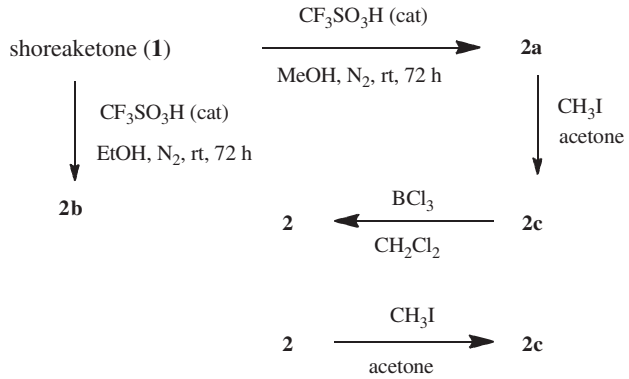
A skeletal rearrangement of stilbenoids offers important information for determination of a stereostructure. Takaya et al. determined the absolute stereostructures of resveratrol dimers ((+)-ampelopsin A, (+)-ampelopsin B, (+)-ampelopsin D, (+)-ampelopsin F) and tetramers ((+)-hopeaphenol, (−)-isohopeaphenol, (+)-vitisin A and (+)-vitisin D) isolated from Vitaceaeous plants by acid- and peroxidase-catalyzed reactions of

Table 5
ROESY data of **1**[a]

No. (^{1}H)	**1** and **1b**	**1**	**1**
H-2a,6a	H-7a, H-8a, H-14a		
H-7a	H-2a,6a, H-14a		
H-8a	H-2a,6a, H-14a,[b] H-7b		
H-12a	OH-13a[c]		
H-14a	H-2a,6a, H-7a, H-8a,[b] OH-13a[c]		
H-2b	H-3b(α), H-3b(α), H-8b, H-7c	H-14c	H-8d,[b] H-10d[b]
H-3b(α)	H-2b		
H-3b(β)	H-2b, H-7c		
H-6b	H-7b		
H-7b	H-8a, H-6b		
H-8b	H-2b, H-14b	H-14c	H-8d
H-12b	OH-13b[c]		
H-14b	H-8b, H-8c, OH-13b[c]	H-14c, H-10d, H-14d	H-3d,5d, H-8d
H-2c		H-7c[c]	
H-3c		H-7c,[c] H-8c[c]	
H-7c	H-2b, H-3b(β)	H-2c,[c] H-3c,[c] H-14c	H-10d
H-8c	H-14b	H-3c,[c] H-8d, H-10d, H-14d	H-14c
H-12c			OH-13c[c]
H-14c		H-2b, H-8b, H-14b, H-7c	H-8c, OH-13c[c]
H-2d,6d	H-7d, H-8d	H-10d, H-14d	
H-3d,5d		OH-4d[c]	H-14b
H-7d	H-2d,6d, H-14d	H-10d	
H-8d	H-2d,6d, H-10d, H-14d	H-8c	H-2b[b], H-8b, H-14b
H-10d	H-8d, OH-11d[c]	H-14b, H-8c, H-2d,6d, H-7d	H-2b,[b] H-7c
H-12d	OH-11d,[c] OH-13d[c]		
H-14d	H-7d, H-8d, OH-13d[c]	H-14b, H-8c, H-2d,6d	
OH-13a	H-12a,[c] H-14a[c]		
OH-13b	H-12b,[c] H-14b[c]		
OH-13c			H-12c, H-14c[c]
OH-4d		H-3d,5d[c]	
OH-11d	H-10d,[c] H-12d[c]		
OH-13d	H-12d,[c] H-14d[c]		

[a] In acetone-d_6 at 600 MHz. Correlations were observed both at rt and −20 °C, unless noted otherwise.
[b] Weak correlations.
[c] Correlations at −20 °C.

(+)-ε-viniferin.[17,18] We noted that the acid-catalyzed skeletal rearrangement of **1** gave mono alkyl ether derivatives of (+)-isohopeaphenol (**2**)[13,19,20] in high stereo peculiarity. Trifluoromethane sulfonic acid or sulfuric acid is used as an acidic additive. When a mixture of shoreaketone (**1**) with each acid in dry MeOH was kept at rt for 18 h and the resulting mixtures purified by preparative TLC, monomethyl ether (**2a**) was obtained in almost quantitative yield. Monoethyl ether (**2b**) was also obtained when the mixture of **2** was reacted with trifluoromethane sulfonic acid in EtOH. The structures of products were confirmed by combined analyses of its ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HMBC, ^{13}C,^{1}H-COSY, and ^{1}H,^{1}H-NOESY spectra. The detailed structural elucidation of **2a** is described in Supplementary data. On the other hand, (+)-isohopeaphenol (**2**) and (−)-hopeaphenol[15] were unchanged even when each compound was treated under more aggressive conditions (trifluoromethane sulfonic acid in CH_3NO_2). This reaction proceeded by cleavages of a C–C bond and an ether bond of the skeleton, and produced another C–C bond. This rearrangement maintains the stereostructure related to the 1,6,7,11b-tetrahydro-4,8,10-trihydroxy-benzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran skeleton in unit **1A**. When **2a** was treated with CH_3I, a permethyl ether **2c** was obtained. The ^{1}H NMR spectrum and $[\alpha]_D$ value of the product (**2c**) was superimposed on those prepared from (+)-isohopeaphenol (**2**). When **2a** was treated with BCl_3, **2** was obtained. In the case of **2**, two identical dimers (hemsleyanol A's[12]) are coupled through a C–C bond of C(8b)–C(8c). Half signals of the total atom numbers can be observed in the ^{1}H and ^{13}C NMR spectrum. The $[\alpha]_D$ value implied that **2** is not a *meso* form. From these evidences, the identity of configurations in two dihydrobenzofuran rings has been demonstrated, and the structural elucidation of **1** described above was further reinforced (Scheme 1).



Scheme 1. Skeletal conversion and functional derivation of **1**.

On the basis of these facts, the formation of isohopeaphenol (**2**) in the reaction of shoreaketone (**1**) with trifluoromethane sulfonic acid can be reasonably explained by virtue of a formation of a methoxydiene intermediate (**E**) via hemiketal (**D**). The subsequent intramolecular cyclization induced by the nucleophilic attack of the π-electron of an electron-rich resorcinol ring to the benzylic position (C-7c) (**F**) and the re-aromatization of the resorcinol ring (**G**) leads to **2a** as the ultimate product (Scheme 2). The neighboring stereo relation of C-10d/C-7c and S_N2 reaction explains the high regio- and stereoselective skeletal transformation.

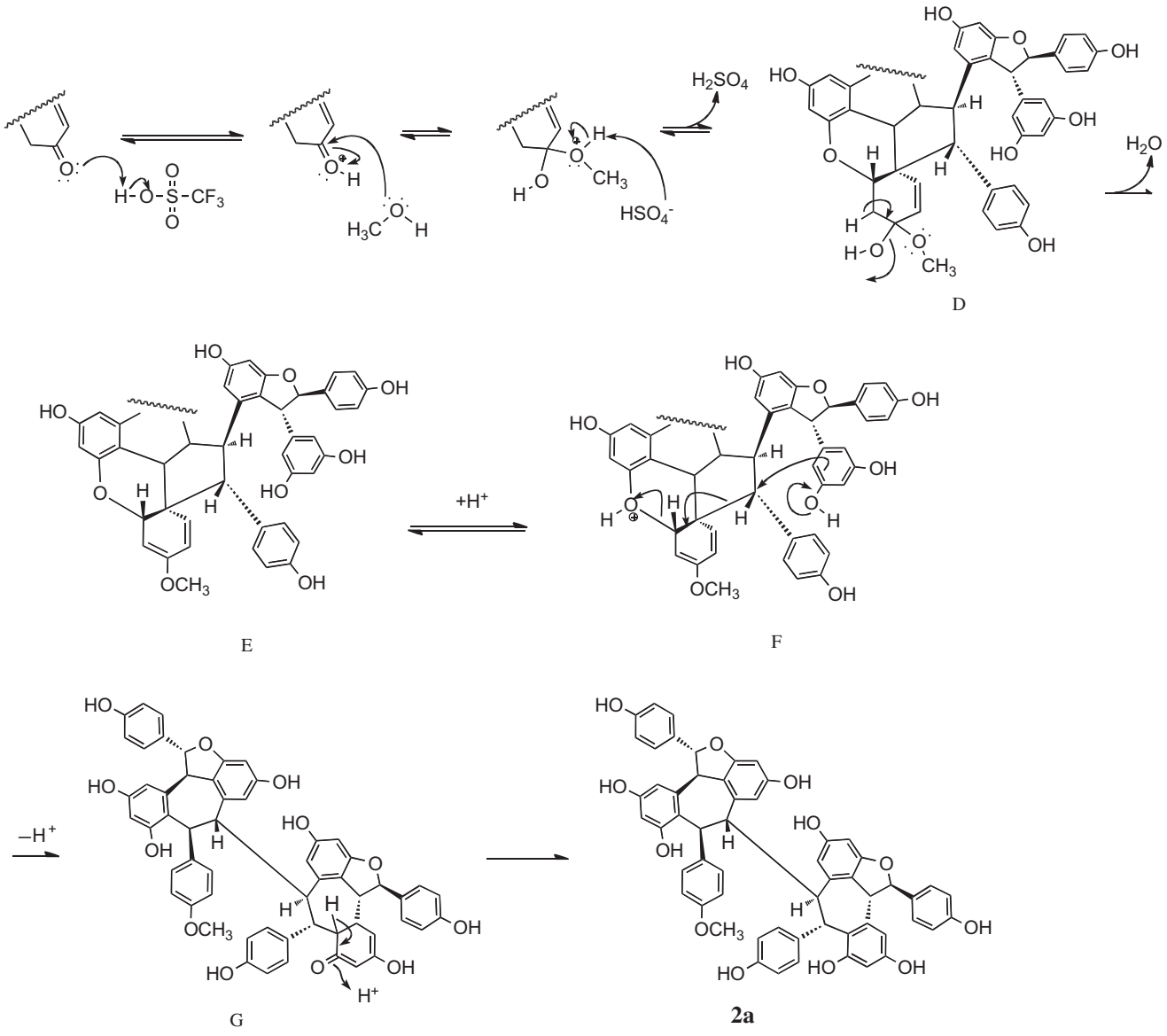
2.5. Absolute structure of shoreaketone

The absolute configuration of two 1,2-diaryl-dihydrobenzofuran chiral centers of (−)-isohopeaphenol have been determined by Takaya et al.[18] On the basis of the absolute configuration of (+)-isohopeaphenol (**2**)[13] and the transformation reaction mechanisms of shoreaketone (**1**) shown above, the absolute configurations of **1** were clearly determined.

2.6. Rotational conformation analysis by NMR study

Shoreaketone (**1**) showed conformational change in solution, and two sets of conformers (**1a** and **1b**) appeared in the NMR spectra. To clarify their conformational properties, the direction of the 2,3-diaryl-dihydrobenzofuran ring (**1B**) in each conformer was determined by ROE correlations (Fig. 2). ROE correlations were observed between H-14c/H-7c and H-14c/H-8b in **1a** and H-14c/H-8c in **1b**. Conversely, no correlations were noted between H-14c/H-8c in **1a** and between H-14c/H-7c and H-14c/H-8b in **1b**. These results suggested that the bond C-9c–C-14c is situated in *syn* to H-7c and H-8b in **1a** and in *syn* to H-8c in **1b**. Supporting ROE evidences in each conformer are correlations between H-14b/H-10d,14d, H-14b/H-14c, H-8c/H-8d, and H-8c/H-10d,14d in **1a** and H-14b/H-2d,6d, H-14b/H-8d, and H-7c/H-10d,14d in **1b**. These results strongly indicated that rotational isomerism is due to restricted rotation of the C–C bond (C-8c/C-9c).

An important feature of the rotational isomerism in the free phenol **1** was the 'rotational conformation exchange' first noted in the NOESY experiment of **1** when recorded in acetone-d_6 at rt. This



Scheme 2. A plausible mechanism for the transformation of shoreaketone (**1**) to methyl ether of (+)-isohopeaphenol (**2a**).

unusual NOE phenomenon was first reported by Hatano et al. in two conformers of procyanidin dimers.[18] The spectrum showed that strong cross peaks represents conformational exchange in which correlations between the same protons in each of the two rotameric isomers dominate the spectrum. This effect was explored further in differential NOE experiments, which clearly showed that despite sharp signals for each of the two rotamers, the effect of irradiation of a proton in one rotamer was translated to the same proton in the other rotamer, indicating that there is rotational interchange between two conformers in the timescale of this experiment. The cross peaks attributable to conformational exchange, for example, was observed between H-14c of **1a** and H-14c of **1b** in the NOESY spectrum (Fig. S2). The translated irradiation was observed when H-14c of **1a** was irradiated, H-14c of **1b** was enhanced, and vice versa, in the differential NOE spectrum. The observation of irradiation transfer requires sufficient difference in chemical shift at respective resolutions. In the case of **1**, the chemical shift of H-14c, H-7d, and H-8d in each rotamer is sufficiently separated in the ^{1}H NMR spectrum, which visualizes the cross peaks in the NOESY spectrum and the irradiation transfers in the differential NOE spectrum.

The extended rotamer conformation (**1a**), in which the C–C bond of C-9c/C-14c was directed to the β-side of the reference plane, was predominant in **1** in organic solvents. In **1a**, the units **1A** and **1B** lie horizontally and the molecule is in an extended form. The compact rotamer conformation (**1b**), in which the C–C bond of C-9c/C-14c was facing the α-side of the reference plane, was inferior in **1**. The units **1A** and **1B** lie vertically and the molecule is in a compact form in **1b** (Fig. 3).

2.7. Chemical shift properties of rotational conformers

The chemical shifts of the particular protons and carbons were markedly different between **1a** and **1b**. This could be explained by the anisotropic shielding/deshielding effects of the aromatic rings. The important matters observed in the ^{1}H NMR spectrum in acetone-d_6 at −20 °C are as follows (Fig. 3). In **1a**, H-8d was observed at δ_H 3.24, whereas that of **1b** was at 4.61. A similar behavior of proton signals was also observed for H-7d (δ_H 4.90 for **1a**; 5.20 for **1b**) and H-2d,6d (δ_H 6.68 for **1a**; 7.19 for **1b**). These data and the configuration of **1a** and **1b** described above explain reasonably well the anisotropy effect of ring C_1 on these protons. The anisotropic effect

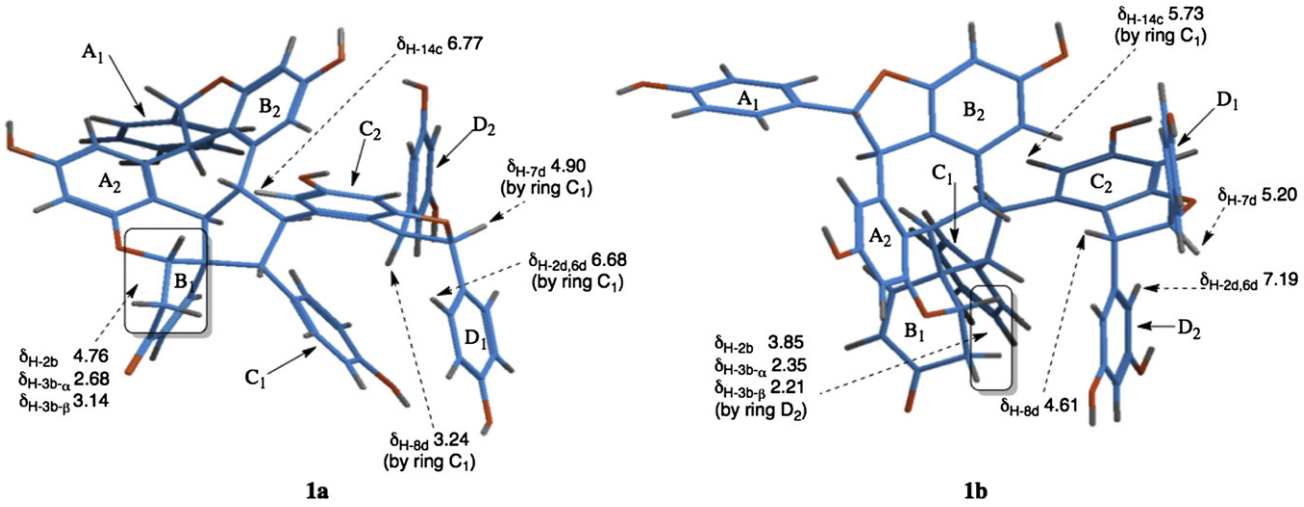


Fig. 3. Stereostructure and shielding of protons by anisotropy in **1a** and **1b**. Energy-minimized conformations of the two rotamers were generated using the MMFF94 force field (MM2 type). Factors of anisotropy are given in parentheses.

by ring C_1 was altered to H-14c in **1b**. Namely, H-14c of **1b** was observed at δ_H 5.73, while that of **1a** was at 6.77. The other anisotropic effects in **1b** were caused by ring D_2, which resulted in upfield shift of H-2b (δ_H 3.85 for **1b**; 4.76 for **1a**) and H-3b (δ_H 2.35 (α), 2.21 (β) for **1b**; 2.68 (α), 3.14 (β) for **1a**). In the ^{13}C NMR spectrum in acetone-d_6, the chemical shifts assigned to C-7c and C-8c are quite different between **1a** and **1b**, which appeared at δ_H 63.31 (C-7c) for **1a**, 57.39 (C-7c) for **1b**, 56.99 (C-8c) for **1a**, and 62.65 (C-8c) for **1b**. The reason for this difference is still unclear.

3. Conclusions

We determined the absolute structure of shoreaketone (**1**), i.e., the first occurrence of rotational isomerism among stilbenoids. Our findings demonstrate complex chemical and dynamic behavior in **1**. From detailed spectral data analysis to examine the mutual effect of the hindered rotation around the chiral axis, we demonstrated the presence of two rotamers. Using edited ROESY, NOESY, and differential NOE experiments, we propose that both rotamers exhibit rotational conformation exchanges. The formation of the dimeric dimer molecule, (+)-isohopeaphenol (**2**) solves the stereochemical aspect of **1**. The present study signifies a new dimension in the ongoing research in this field by exploring this type of complex system bearing a 2,3-diaryl-dihydrobenzofuran ring.

4. Experimental

4.1. General

The following instruments were used: a JASCO P-1020 polarimeter for optical rotations; a Shimadzu UV-3100 spectrophotometer (in MeOH solution) for UV spectroscopy; a JASCO J-820 spectrometer (in MeOH solution) for CD spectroscopy; a JEOL JNM ECA-600, AL-400, EX-400, and LA-300 spectrometer for ^1H and ^{13}C NMR spectroscopy (chemical shift values in ^1H NMR spectra were presented as™ values with TMS as the internal standard); JEOL-JMS-T100 LC mass spectrometer mass spectrometer for ESIMS; and JEOL JMS-DX-300 instrument for FABMS. The following adsorbents were used for purification: Merck Kieselgel 60 F_{254} (0.25 mm) for analytical TLC; Merck Kieselgel 60, Fuji Silysia Chemical Chromatorex, and Waters Sep-Pak C18 cartridges for column chromatography; a Capcell Pak C18 column (UG120, 250×10 mm i.d., SHISEIDO, Japan) for preparative HPLC; and CHIRALPAK IB and OJ-RH columns (each 150×4.6 mm i.d., Daicel Chemical Industries Ltd., Japan) for enantiomeric separation by HPLC.

4.2. Plant material

Stem barks of *S. uliginosa* (Foxw) and *S. hemsleyana* were collected in India in October 1997. The stem bark of *V. indica* was collected in India in June 2004. Voucher specimens DP-004 (*S. uliginosa*), DP-003 (*S. hemsleyana*), and DP-031 (*V. indica*) have been deposited at Gifu Pharmaceutical University, Gifu, Japan.

4.3. Extraction and isolation

Dried and ground stem bark (1.2 kg) of *S. uliginosa* was extracted successively with acetone (4 L×24 h×3), MeOH (4 L×24 h×3), and 70% MeOH (4 L×24 h×2) at rt. The extract was concentrated to yield respective residues; 62 g (acetone), 82 g (MeOH), and 43 g (70% MeOH). The acetone extract (60 g) was subjected to column chromatography on silica gel eluted with a mixture of EtOAc/$CHCl_3$/MeOH/H_2O increasing in the polarity to give 57 fractions (Fr. 1–57). Fractions were combined by indication of the Gibbs test on TLC. The combined fractions of fractions 8 to 14 [EtOAc/$CHCl_3$/MeOH/H_2O (160:80:11:2), 1.2 g] were purified by VLC [EtOAc/$CHCl_3$/MeOH/H_2O (80:40:11:2)] to produce **1** (450 mg). The experimental procedure for stem bark of *S. hemsleyana*[12] and *V. indica*[20] has been described in a previous report. Each of these two sources provided **1** (120 mg from *S. hemsleyana* and 25 mg from *V. indica*).

*4.3.1. Shoreaketone (**1**; **1a**,**b**).* A yellow amorphous solid; solid; mp 256–258 °C (decomp.); $[\alpha]_D^{25}$ −225 (*c* 0.1, MeOH); CD (*c* 22.1 μM, MeOH) nm (Δε): 237 (−96.9), 261 (−11.3), 272 (−19.2), 299 (+4.9) (Fig. S5); UV (MeOH) λ_{max} (log ε): 285 (4.14), 292sh (4.08) nm; IR ν (KBr disk): 3400, 2920, 2851, 1743, 1660, 1616, 1598, 1516, 1453, 1340, 1244, 1173, 1153, 1022, 999, 834 cm^{-1}; Positive ion ESIMS *m*/*z*: 929 $[M+Na]^+$; Positive ion HRESIMS *m*/*z*: 929.2610 $[M+Na]^+$ (calcd 929.2574 for $C_{56}H_{42}O_{12}Na$); Negative ion FABMS *m*/*z*: 905 $[M-H]^-$; The ^1H and ^{13}C NMR spectral data at rt: see literature; The ^1H and ^{13}C NMR spectral data at −20 °C: Tables 2 and 3, respectively; HMBC and NOESY* correlations: Tables 4 and 5, respectively. *Selected correlations are designated in the literature[11] and Fig. 1.

*4.3.2. Methylation of **1**.* Shoreaketone (**1**) (20 mg) was reacted with K_2CO_3 (200 mg) and MeI (20 mg) in dry acetone under reflux for 5 h. The reaction mixture was treated in the usual manner and the

crude product (24 mg) obtained was purified by preparative TLC (*n*-hexane/EtOAc 1:1) to afford permethyl ether (**1c**,**d**) (20 mg).

*4.3.3. Shoreaketone permethyl ether (**1c**,**d**).* A pale yellow solid; $[\alpha]_D^{25}$ −280 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε): 285 (4.19), 292sh (4.12) nm; Positive ion ESIMS *m*/*z*: 1041 $[M+Na]^+$; Positive ion HRESIMS *m*/*z*: 1041.3821 $[M+Na]^+$ (calcd 1041.3820 for $C_{64}H_{58}O_{12}Na$); ^1H NMR for **1c** [400 MHz, acetone-d_6] δ: 7.61 (2H, d, *J*=8.8 Hz, H-2a,6a), 7.03 (2H, d, *J*=8.8 Hz, H-3a,5a), 6.03 (1H, d, *J*=9.8 Hz, H-7a), 5.13 (1H, d, *J*=9.8 Hz, H-8a), 6.28 (1H, d, *J*=2.0 Hz, H-12a), 6.57 (1H, br s, H-14a), 4.93 (1H, br s, H-2b), 2.71(1H, dd, *J*=15.1, 2.2 Hz, H-3b(α)), 3.10 (1H, dd, *J*=15.1, 0.9 Hz, H-3b(β)), 5.45 (1H, d, *J*=10.2 Hz, H-5b), 6.62 (1H, dd, *J*=10.2, 2.4 Hz, H-6b), 3.91 (1H, H-7b)*, 3.68 (1H, H-8b)*, 6.06 (1H, d, *J*=2.0 Hz, H-12b), 5.73 (1H, d, *J*=2.0 Hz, H-14b), 3.46 (1H, d, *J*=10.4 Hz, H-7c), 3.89 (1H, H-8c)*, 6.37 (1H, d, *J*=2.0 Hz, H-12c), 6.93 (1H, d, *J*=2.0 Hz, H-14c), 6.67 (2H, d, *J*=8.8 Hz, H-2d,6d), 6.72 (2H, d, *J*=8.8 Hz, H-3d,5d), 5.31 (1H, d, *J*=3.4 Hz, H-7d), 3.54 (1H, d, *J*=3.4 Hz, H-8d), 6.21 (1H, d, *J*=2.0 Hz, H-10d), 6.13 (1H, t, *J*=2.0 Hz, H-12d), 6.21 (1H, d, *J*=2.0 Hz, H-14d), 3.82 (3H, s, OMe-4a), 3.70 (3H, s, OMe-13a), 3.32 (3H, s, OMe-13b), 3.64 (3H, s, OMe-4c), 3.85 (3H, s, OMe-13c), 3.78 (3H, s, OMe-4d), 3.70 (3H, s, OMe-11d), 3.70 (3H, s, OMe-13d). H-2c, H-3c, H-5c, and H-6c were not identified (*Masked by neighboring peaks and J-values were not clear. Assignments were obtained from $^1H-^1H$ COSY and $^{13}C-^1H$ COSY correlations); ^{13}C NMR for **1c** [100 MHz, acetone-d_6] δ: 134.1 (C-1a), 129.6 (C-2a,6a), 114.8 (C-3a,5a), 161.1 (C-4a), 86.9 (C-7a), 51.4 (C-8a), 143.2 (C-9a), 114.6 (C-10a), 155.5 (C-11a), 99.9 (C-12a), 160.6 (C-13a), 105.6 (C-14a), 46.1 (C-1b), 76.8 (C-2b), 40.4 (C-3b), 195.9 (C-4b), 129.7 (C-5b), 154.1 (C-6b), 48.6 (C-7b), 50.4 (C-8b), 137.7 (C-9b), 118.1 (C-10b), 160.4 (C-11b), 95.6 (C-12b), 160.8 (C-13b), 106.7 (C-14b), 132.8 (C-1c), 159.8 (C-4c), 63.6 (C-7c), 57.6 (C-8c), 142.8 (C-9c), 124.3 (C-10c), 161.7 (C-11c), 95.1 (C-12c), 163.1 (C-13c), 105.5 (C-14c), 134.8 (C-1d), 128 (C-2d,6d), 115.2 (C-3d,5d), 160.6 (C-4d), 93.9 (C-7d), 55.7 (C-8d), 147.2 (C-9d), 106.4 (C-10d), 162 (C-11d), 99.1 (C-12d), 162 (C-13d), 106.4 (C-14d), 55.9 (OMe-4a), 55.7 (OMe-13a), 54.8 (OMe-13b), 55.5 (OMe-4c), 56.2 (OMe-13c), 55.6 (OMe-4d), 55.7 (OMe-11d), 55.7 (OMe-13d). C-2c, C-3c, C-5c, and C-6c were not identified; COLOC correlations for **1c**: C-1a/H-3a,5a, C-1a/H-8a, C-2a,6a/H-7a, C-4a/H-2a,6a, C-4a/OMe-4a, C-8a/H-14a, C-9a/H-7a, C-9a/H-8a, C-9a/H-7b, C-10a/H-12a, C-10a/H-14a, C-10a/H-7b, C-11a/H-12a, C-11a/H-7b, C-12a/H-14a, C-13a/H-12a, C-13a/H-14a, C-13a/OMe-13a, C-14a/H-12a, C-1b/H-3b(α), C-1b/H-5b, C-1b/H-7b, C-1b/H-7c, C-2b/H-3b(α), C-2b/H-6b, C-2b/H-7b, C-2b/H-7c, C-4b/H-2b, C-4b/H-3b(α), C-4b/H-3b(β), C-4b/H-6b, C-5b/H-3b(α), C-6b/H-2b, C-6b/H-7b, C-7b/H-6b, C-7b/H-8b, C-8b/H-7b, C-8b/H-14b, C-9b/H-7b, C-9b/H-8b, C-10b/H-8a, C-10b/H-12b, C-10b/H-14b, C-11b/H-12b, C-12b/H-14b, C-13b/H-12b, C-13b/H-14b, C-13b/OMe-13b, C-14b/H-12b, C-14b/H-8b, C-1c/H-7c, C-4c/OMe-4c, C-7c/C-8c, C-8c/C-8b, C-8c/C-14c, C-9c/H-8b, C-9c/H-7c, C-9c/H-8c, C-9c/H-8d, C-10c/H-12c, C-10c/H-14c, C-10c/H-8d, C-11c/H-12c, C-12c/H-14c, C-13c/H-12c, C-13c/H-14c, C-13c/OMe-13c, C-14c/H-8c, C-14c/H-12c, C-1d/H-3d,5d, C-1d/H-7d, C-1d/H-8d, C-2d,6d/H-7d, C-4d/H-2d,6d, C-4d/OMe-4d, C-7d/H-8d, C-8d/H-10d, C-8d/H-14d, C-9d/H-7d, C-9d/H-8d, C-10d/H-8d, C-10d/H-12d, C-10d/H-14d, C-11d/H-12d, C-11d/OMe-11d, C-12d/H-10d, C-12d/H-14d, C-13d/H-12d, C-13d/OMe-13d, C-14d/H-8d, C-14d/H-10d, C-14d/H-12d; ^1H NMR for **1d** [400 MHz, acetone-d_6] δ: 7.60 (2H, d, *J*=8.8 Hz, H-2a,6a), 6.93 (2H, d, *J*=8.8 Hz, H-3a,5a), 6.04 (1H, d, *J*=9.8 Hz, H-7a), 5.13 (1H, d, *J*=9.8 Hz, H-8a), 3.91 (1H, H-2b), 2.32 (1H, br d, *J*=15.2 Hz, H-3b(α)), 2.14 (1H, br d, *J*=15.2 Hz, H-3b(β)), 5.32 (1H, H-5b), 6.40 (1H, H-6b)*, 6.04 (1H, H-12b)*, 5.89 (1H, d, *J*=2.0 Hz, H-14b), 7.33 (2H, d, *J*=8.8 Hz, H-2d,6d), 6.78 (2H, d, *J*=8.8 Hz, H-3d,5d), 5.40 (1H, d, *J*=2.0 Hz, H-7d), 5.00 (1H, d, *J*=2.0 Hz, H-8d). H-12a, H-14a, H-7b, H-8b H-7c, H-8c, H-12c, H-14c, H-10d, H-12d, and H-14d were not identified because they were obscured by neighboring peaks. H-2c, H-3c, H-5c, and H-6c were not identified (*Masked by neighboring peaks and J-values were not clear. Assignments were obtained from $^1H-^1H$ COSY and $^{13}C-^1H$ COSY correlations).

*4.3.4. Acetylation of **1**.* Shoreaketone (**1**) (30 mg) was dissolved in a mixture of pyridine (2.0 mL) and Ac_2O (0.2 mL). The reaction mixture was kept at rt for 24 h. The solution was treated with the usual manner and the resulting crude product (35 mg) was purified by prep. TLC with *n*-hexane/EtOAc 1:1 to afford peracetate (**1e**) (32 mg).

*4.3.5. Shoreaketone peracetate (**1e**).* A pale yellow solid; $[\alpha]_D^{25}$ −192 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε): 281 (4.01), 288sh (4.00) nm; Positive ion ESIMS *m*/*z*: 1265 $[M+Na]^+$; Positive ion HRESIMS *m*/*z*: 1265.3389 $[M+Na]^+$ (calcd 1265.3414 for $C_{72}H_{58}O_{20}Na$); ^1H NMR [400 MHz, $CDCl_3$] δ: 7.52 (2H, d, *J*=8.8 Hz, H-2a,6a), 7.18 (2H, d, *J*=8.8 Hz, H-3a,5a), 6.17 (1H, d, *J*=8.3 Hz, H-7a), 4.89 (1H, d, *J*=8.3 Hz, H-8a), 6.54 (1H, d, *J*=2.0 Hz, H-12a), 6.73 (1H, br s, H-14a), 4.59 (1H, br s, H-2b), 2.87(1H, dd, *J*=15.1, 2.2 Hz, H-3b(α)), 2.80 (1H, dd, *J*=15.1, 0.9 Hz, H-3b(β)), 5.68 (1H, d, *J*=10.0 Hz, H-5b), 6.52 (1H, dd, *J*=10.0, 2.4 Hz, H-6b), 3.75 (1H, d, *J*=11.4 Hz, H-7b), 3.37 (1H, t, *J*=11.4 Hz, H-8b), 6.41 (1H, d, *J*=2.2 Hz, H-12b), 5.90 (1H, d, *J*=2.2 Hz, H-14b), 3.12 (1H, d, *J*=9.7 Hz, H-7c), 3.43 (1H, dd, *J*=11.4, 9.7 Hz, H-8c), 6.56 (1H, d, *J*=2.0 Hz, H-12c), 6.75 (1H, d, *J*=2.0 Hz, H-14c), 6.86 (2H, d, *J*=8.8 Hz, H-2d,6d), 6.95 (2H, d, *J*=8.8 Hz, H-3d,5d), 5.39 (1H, d, *J*=6.4 Hz, H-7d), 3.29 (1H, d, *J*=6.4 Hz, H-8d), 6.60 (1H, d, *J*=2.2 Hz, H-10d), 6.37 (1H, t, *J*=2.2 Hz, H-12d), 6.60 (1H, d, *J*=2.2 Hz, H-14d), 2.18 (9H, s, OAc), 2.24 (3H, s, OAc), 2.25 (3H, s, OAc), 2.27 (3H, s, OAc), 2.29 (3H, s, OAc), 2.32 (3H, s, OAc); ^{13}C NMR [100 MHz, $CDCl_3$] δ: 138.8 (C-1a), 126.7 (C-2a,6a), 121.8 (C-3a,5a), 150.47 (C-4a), 84 (C-7a), 50.8 (C-8a), 141.3 (C-9a), 117.8 (C-10a), 153.8 (C-11a), 108.9 (C-12a), 150.1 (C-13a), 109.7 (C-14a), 44 (C-1b), 75.7 (C-2b), 38.5 (C-3b), 195 (C-4b), 129.7 (C-5b), 151.5 (C-6b), 46.5 (C-7b), 49 (C-8b), 135.2 (C-9b), 121.9 (C-10b), 158.7 (C-11b), 102.5 (C-12b), 150.9 (C-13b), 114.3 (C-14b), 136 (C-1c), 130.5 (C-2c), 121.3 (C-3c), 149.9 (C-4c), 121.3 (C-5c), 130.5 (C-6c), 62.7 (C-7c), 56 (C-8c), 139.7 (C-9c), 126.78 (C-10c), 160.3 (C-11c), 102.7 (C-12c), 152.5 (C-13c), 112.2 (C-14c), 137.5 (C-1d), 126.81 (C-2d,6d), 121.7 (C-3d,5d), 150.52 (C-4d), 92.3 (C-7d), 55.5 (C-8d), 143.3 (C-9d), 119.3 (C-10d), 150.7 (C-11d), 113.1 (C-12d), 150.7 (C-13d), 119.3 (C-14d), 168.4 (C=O−OAc), 168.96 (C=O−OAc), 168.98 (C=O−OAc), 169.11 (C=O−OAc), 169.11 (C=O−OAc), 169.15 (C=O−OAc), 169.17 (C=O−OAc), 169.24 (C=O−OAc), 21.0 (Me−OAc); COLOC correlations for **1e**: C-8a/H-14a, C-9a/H-7a, C-9a/H-8a, C-9a/H-7b, C-10a/H-12a, C-10a/H-14a, C-10a/H-7b, C-11a/H-12a, C-11a/H-7b, C-12a/H-14a, C-13a/H-12a, C-13a/H-14a, C-14a/H-12a, C-1b/H-3b(a), C-1b/H-5b, C-1b/H-7b, C-1b/H-7c, C-2b/H-3b(a), C-2b/H-6b, C-2b/H-7b, C-2b/H-7c, C-4b/H-2b, C-4b/H-3b(a), C-4b/H-3b(b), C-4b/H-6b, C-5b/H-3b(a), C-6b/H-2b, C-6b/H-7b, C-7b/H-6b, C-7b/H-8b, C-8b/H-7b, C-8b/H-14b, C-9b/H-7b, C-9b/H-8b, C-10b/H-8a, C-10b/H-12b, C-10b/H-14b, C-11b/H-12b, C-12b/H-14b, C-13b/H-12b, C-13b/H-14b, C-14b/H-12b, C-14b/H-8b, C-1c/H-7c, C-7c/C-8c, C-8c/C-8b, C-8c/C-14c, C-9c/H-8b, C-9c/H-7c, C-9c/H-8c, C-9c/H-8d, C-10c/H-12c, C-10c/H-14c, C-10c/H-8d, C-11c/H-12c, C-12c/H-14c, C-13c/H-12c, C-13c/H-14c, C-14c/H-8c, C-14c/H-12c, C-1d/H-3d,5d, C-1d/H-7d, C-1d/H-8d, C-2d,6d/H-7d, C-4d/H-2d,6d, C-7d/H-8d, C-8d/H-10d, C-8d/H-14d, C-9d/H-7d, C-9d/H-8d, C-10d/H-8d, C-10d/H-12d, C-10d/H-14d, C-11d/H-12d, C-12d/H-10d, C-12d/H-14d, C-13d/H-12d, C-14d/H-8d, C-14d/H-10d, C-14d/H-12d; NOESY correlations: H-2a,6a/H-7a, H-2a,6a/H-8a, H-2a,6a/H-14a, H-7a/H-2a,6a, H-7a/H-14a, H-8a/H-2a,6a, H-8a/H-7b, H-14a/H-2a,6a, H-14a/H-7a, H-2b/H-3b(a), H-2b/H-3b(b), H-2b/H-7c, H-3b(a)/H-2b, H-3b(b)/H-2b, H-6b/H-7b, H-7b/H-8a, H-7b/H-6b, H-8b/H-7c, H-8b/H-14c, H-14b/H-14c, H-14b/H-10d,14d, H-7c/H-2b, H-7c/H-8b, H-7c/H-14c, H-14c/H-14b, H-14c/H-8b, H-14c/H-7c, H-2d,6d/H-7d, H-2d,6d/H-8d, H-

7d/H-2d,6d, H-7d/H-10d,14d, H-8d/H-2d,6d, H-8d/H-10d,14d, H-10d,14d/H-14b, H-10d,14d/H-7d, H-10d,14d/H-8d.

*4.3.6. Deacetylation of **1e**.* Shoreaketone peracetate (**1e**) (5 mg) was kept at 80 °C for 4 h with 2 M NaOH (10 mL) and MeOH (10 mL). The reaction mixture was neutralized with H_2SO_4 and extracted with EtOAc. The resulting solid was purified with PTLC [EtOAc/$CHCl_3$/MeOH/H_2O 80:40:11:2] to afford **1** (4 mg).

*4.3.7. Preparation of hydrazone of **1**.* 2-Chloro-4.6-dinitrophenyl hydrazine (35 mg) was added in 2 drops of sulfuric acid and 10 mL of EtOH, and heated on a boiling water bath until hydrazine was dissolved. After cooling, **1** (100 mg) in 2 mL of EtOH and 1 mL of water was added to the solution. After 24 h, the solution was purified by column chromatography on silica gel with $CHCl_3$/MeOH (10:1) as an eluent to obtain phenylhydrazone derivative. An orange solid; Positive ion ESIMS *m*/*z*: 1143 $[M+Na]^+$; Positive ion HRESIMS *m*/*z*: 1143.2466 $[M+Na]^+$ (calcd 1143.2462 for $C_{62}H_{45}O_{15}N_4ClNa$).

*4.3.8. Acidic conversion of shoreaketone (**1**).* A mixture of shoreaketone (**1**) (5 mg) and trifluoromethane sulfonic acid (2.0 μL) in MeOH (1.0 mL) was stirred under an atmosphere of nitrogen at rt for 18 h. The reaction mixture was diluted by water (10 mL) and extracted with ethyl acetate (10 mL×2). The extract was dried over anhydrous sodium sulfate. After solvent evaporation, the residue was subjected to prep. TLC (EtOAc/$CHCl_3$/MeOH/H_2O 80:40:11:2) to give **2a** (4.8 mg). A reaction in EtOH gave **2b** (1 mg).

*4.3.9. Demethylation of **2a**.* To a solution of dry CH_2Cl_2 (30 mL) containing **2a** (2 mg) BCl_3 was added (0.5 mL) at −25 °C. The reaction mixture was left at rt for 6 h and evaporated under reduced pressure. The residue was purified by prep. TLC (EtOAc/$CHCl_3$/MeOH/H_2O 80:40:11:2) to give **2** (1.6 mg).

*4.3.10. (+)-Isohopeaphenol monomethyl ether (**2a**).* A pale yellow solid; $[\alpha]_D^{25}$ +214 (*c* 0.1, MeOH); CD (*c* 21.7 μM, MeOH) nm (Δε): 241 (−51.1), 263 (+19.2), 274 (+16.5), 288 (+29.3) (Fig. S5); Positive ion ESIMS *m*/*z*: 943 $[M+Na]^+$; Positive ion HRESIMS *m*/*z*: 943.2712 $[M+Na]^+$ (calcd 943.2725 for $C_{57}H_{44}O_{12}Na$); ^1H NMR [400 MHz, acetone-d_6] δ: 7.54 (2H, d, *J*=8.8 Hz, H-2a,6a)[(a)], 7.00 (2H, d, *J*=8.8 Hz, H-3a,5a)[(b)], 8.00 (1H, br s, OH-4a)[(J)], 5.65 (1H, d, *J*=10.2 Hz, H-7a)[(k)], 5.45 (1H, br d, *J*=10.2 Hz, H-8a)[(l)], 8.65 (1H, br s, OH-11a)[(c)], 6.38 (1H, d, *J*=2.2 Hz, H-12a)[(d)], 8.14 (1H, br s, OH-13a)[(e)], 6.31 (1H, d, *J*=2.2 Hz, H-14a)[(f)], 6.48 (2H, d, *J*=8.6 Hz, H-2b,6b), 6.43 (2H, d, *J*=8.6 Hz, H-3b,5b), 5.19 (1H, br s Hz, H-7b), 3.47 (1H, br s Hz, H-8b)[(g)], 5.85 (1H, d, *J*=2.2 Hz, H-12b)[(h)], 7.71 (1H, br s, OH-13b)[(i)], 5.51 (1H, d, *J*=2.2 Hz, H-14b)[(m)], 6.40 (2H, d, *J*=8.6 Hz, H-2c,6c), 6.35 (2H, d, *J*=8.6 Hz, H-3c,5c), 7.76 (1H, br s, OH-4c), 5.17 (1H, br s Hz, H-7c), 3.47 (1H, br s Hz, H-8c)[(g)], 5.85 (1H, d, *J*=2.2 Hz, H-12c)[(h)], 7.71 (1H, br s, OH-13c)[(i)], 5.52 (1H, d, *J*=2.2 Hz, H-14c)[(m)], 7.54 (2H, d, *J*=8.8 Hz, H-2d,6d)[(a)], 7.00 (2H, d, *J*=8.8 Hz, H-3d,5d)[(b)], 7.96 (1H, br s, OH-4d)[(J)], 5.66 (1H, d, *J*=10.2 Hz, H-7d)[(k)], 5.44 (1H, br d, *J*=10.2 Hz, H-8d)[(l)], 8.65 (1H, br s, OH-11d)[(c)], 6.38 (1H, d, *J*=2.2 Hz, H-12d)[(d)], 6.31 (1H, d, *J*=2.2 Hz, H-14d)[(f)], 3.58 (3H, s, OMe-4b). (a)–(i): overlapping. (j)–(m): interchangeable; ^{13}C NMR for **2a** [100 MHz, acetone-d_6] δ: 133.54 (C-1a)[(a)], 130.5 (C-2a,6a)[(i)], 116.3 (C-3a,5a)[(j)], 158.3 (C-4a)[(k)], 93.3 (C-7a)[(l)], 53.53 (C-8a)[(b)], 140.5 (C-9a)[(m)], 117.9 (C-10a)[(c)], 158.2 (C-11a)[(n)], 102.2 (C-12a)[(o)], 156.59 (C-13a)[(d)], 106.9 (C-14a)[(p)], 138.5 (C-1b), 129.6 (C-2b,6b)[(q)], 112.9 (C-3b,5b), 157.5 (C-4b), 52.5 (C-8b)[(e)], 141.3 (C-9b)[(f)], 116.7 (C-10b)[(s)], 160.2 (C-11b)[(t)], 95.1 (C-12b)[(g)], 158 (C-13b)[(u)], 109.4 (C-14b)[(h)], 137.1 (C-1c), 129.6 (C-2c,6c)[(q)], 114.4 (C-3c,5c), 154.9 (C-4c), 43.3 (C-7c)[(r)], 52.4 (C-8c)[(e)], 141.4 (C-9c)[(f)], 116.7 (C-10c)[(s)], 160.2 (C-11c)[(t)], 95 (C-12c)[(g)], 158 (C-13c)[(u)], 109.3 (C-14c)[(h)], 133.49 (C-1d)[(a)], 130.5 (C-2d,6d)[(i)], 116.3 (C-3d,5d)[(j)], 158.3 (C-4d)[(k)], 93.3 (C-7d)[(l)], 53.45 (C-8d)[(b)], 140.5 (C-9d)[(m)], 117.8 (C-10d)[(c)], 158.2 (C-11d)[(n)], 102.2 (C-12d)[(o)], 156.56 (C-13d)[(d)], 106.9 (C-14d)[(p)], 54.8 (OMe-4b). (a)–(h): interchangeable. (i)–(u): overlapping; HMBC correlations: H-2a,6a/C-4a, H-2a,6a/C-7a, H-3a,5a/C-1a, H-3a,5a/C-4a, H-7a/C-1a, H-7a/C-2a,6a, H-7a/C-8a, H-7a/C-9a, H-8a/C-1a, H-8a/C-7a, H-8a/C-9a, H-8a/C-10a, H-8a/C-14a, H-8a/C-9b, H-8a/C-10b, H-8a/C-11b, H-12a/C-10a, H-12a/C-11a, H-12a/C-13a, H-12a/C-14a, H-14a/C-8a, H-14a/C-10a, H-14a/C-12a, H-14a/C-13a, H-2b,6b/C-4b, H-2b,6b/C-7b, H-3b,5b/C-1b, H-3b,5b/C-4b, H-7b/C-9a, H-7b/C-10a, H-7b/C-11a, H-7b/C-1b, H-7b/C-2b,6b, H-7b/C-8b, H-7b/C-9b, H-7b/C-8c, H-8b/C-10a, H-8b/C-1b, H-8b/C-7b, H-8b/C-9b, H-8b/C-10b, H-8b/C-14b, H-8b/C-7c, H-8b/C-9c, H-12b/C-10b, H-12b/C-11b, H-12b/C-13b, H-12b/C-14b, H-14b/C-8b, H-14b/C-10b, H-14b/C-12b, H-14b/C-13b, H-2c,6c/C-4c, H-2c,6c/C-7c, H-3c,5c/C-1c, H-3c,5c/C-4c, H-7c/C-8b, H-7c/C-9d, H-7c/C-10d, H-7c/C-11d, H-7c/C-1c, H-7c/C-2c,6c, H-7c/C-8c, H-7c/C-9c, H-8c/C-7b, H-8c/C-9b, H-8c/C-10d, H-8c/C-1c, H-8c/C-7c, H-8c/C-9c, H-8c/C-10c, H-8c/C-14c, H-12c/C-10c, H-12c/C-11c, H-12c/C-13c, H-12c/C-14c, H-14c/C-8c, H-14c/C-10c, H-14c/C-12c, H-14c/C-13c, H-2d,6d/C-4d, H-2d,6d/C-7d, H-3d,5d/C-1d, H-3d,5d/C-4d, H-7d/C-1d, H-7d/C-2d,6d, H-7d/C-8d, H-7d/C-9d, H-8d/C-1d, H-8d/C-7d, H-8d/C-9d, H-8d/C-10d, H-8d/C-14d, H-8d/C-9c, H-8d/C-10c, H-8d/C-11c, H-12d/C-10d, H-12d/C-11d, H-12d/C-13d, H-12d/C-14d, H-14d/C-8d, H-14d/C-10d, H-14d/C-12d, H-14d/C-13d, OH-4a/C-3a,5a, OH-4a/C-4a, OH-11a/C-10a, OH-11a/C-11a, OH-13a/C-12a, OH-13a/C-13a, OH-13a/C-14a, OH-13b/C-12b, OH-13b/C-13b, OH-13b/C-14b, OH-4c/C-3c,5c, OH-4c/C-4c, OH-13c/C-12c, OH-13c/C-13c, OH-13c/C-14c, OH-4d/C-3d,5d, OH-4d/C-4d, OH-11d/C-10d, OH-11d/C-11d, OH-13d/C-12d, OH-13d/C-13d, OH-13d/C-14d, OMe-4b/C-4b; NOESY correlations: H-2a,6a/H-7a, H-2a,6a/H-8a, H-2a,6a/H-14a, H-3a,5a/OH-4a, H-3a,5a/OH-13a, H-3a,5a/OH-11d, H-7a/H-2a,6a, H-7a/H-14a, H-8a/H-2a,6a, H-8a/H-14a, H-8a/H-2c,6c, H-8a/H-8c, H-8a/H-14c, H-12a/OH-11a, H-12a/OH-13a, H-14a/H-2a,6a, H-14a/H-7a, H-14a/H-8a, H-14a/OH-13a, H-2b,6b/H-7b, H-2b,6b/H-8b, H-2b,6b/H-14b, H-2b,6b/H-8d, H-3b,5b/OMe-4b, H-7b/H-2b,6b, H-7b/H-8b, H-8b/H-2b,6b, H-8b/H-7b, H-8b/H-14b, H-8b/H-8d, H-12b/OH-13b, H-14b/H-2b,6b, H-14b/H-8b, H-14b/H-8d, H-14b/OH-13b, H-2c,6c/H-7c, H-2c,6c/H-8c, H-2c,6c/H-14c, H-2c,6c/H-8a, H-3c,5c/OH-4c, H-3c,5c/OH-4d, H-7c/H-2c,6c, H-7c/H-8c, H-8c/H-2c,6c, H-8c/H-7c, H-8c/H-14c, H-8c/H-8a, H-12c/OH-13c, H-14c/H-8a, H-14c/H-2c,6c, H-14c/H-8c, H-14c/OH-13c, H-2d,6d/H-7d, H-2d,6d/H-8d, H-2d,6d/H-14d, H-3d,5d/OH-11a, H-3d,5d/OH-13d, H-7d/H-2d,6d, H-7d/H-14d, H-8d/H-2b,6b, H-8d/H-8b, H-8d/H-14b, H-8d/H-2d,6d, H-8d/H-14d, H-12d/OH-11d, H-12d/OH-13d, H-14d/H-2d,6d, H-14d/H-7d, H-14d/H-8d, H-14d/OH-13d, OH-4a/H-3a,5a, OH-11a/H-12a, OH-11a/H-3d,5d, OH-13a/H-3a,5a, OH-13a/H-12a, OH-13a/H-14a, OH-13b/H-12b, OH-13b/H-14b, OH-4c/H-3c,5c, OH-13c/H-12c, OH-13c/H-14c, OH-4d/H-3c,5c, OH-11d/H-3a,5a, OH-11d/H-12d, OH-13d/H-3d,5d, OH-13d/H-12d, OH-13d/H-14d, OMe-4b/H-3b,5b.

*4.3.11. (+)-Isohopeaphenol monoethyl ether (**2b**).* A pale yellow solid; Positive ion ESIMS *m*/*z*: 957 $[M+Na]^+$; Positive ion HRESIMS *m*/*z*: 957.2870 $[M+Na]^+$ (calcd 957.2881 for $C_{58}H_{46}O_{12}Na$); ^1H NMR [400 MHz, acetone-d_6] δ: 7.54 (2H, d, *J*=8.8 Hz, H-2a,6a)[(a)], 7.00 (2H, d, *J*=8.8 Hz, H-3a,5a)[(b)], 8.00 (1H, br s, OH-4a)[(J)], 5.65 (1H, d, *J*=10.2 Hz, H-7a)[(k)], 5.45 (1H, br d, *J*=10.2 Hz, H-8a)[(l)], 8.60 (1H, br s, OH-11a)[(c)], 6.38 (1H, d, *J*=2.2 Hz, H-12a)[(d)], 8.11 (1H, br s, OH-13a)[(e)], 6.31 (1H, d, *J*=2.2 Hz, H-14a)[(f)], 6.48 (2H, d, *J*=8.6 Hz, H-2b,6b), 6.43 (2H, d, *J*=8.6 Hz, H-3b,5b), 5.19 (1H, br s Hz, H-7b), 3.47 (1H, br s Hz, H-8b)[(g)], 5.85 (1H, d, *J*=2.2 Hz, H-12b)[(h)], 7.66 (1H, br s, OH-13b)[(i)], 5.51 (1H, d, *J*=2.2 Hz, H-14b)[(m)], 6.40 (2H, d, *J*=8.6 Hz, H-2c,6c), 6.35 (2H, d, *J*=8.6 Hz, H-3c,5c), 7.70 (1H, br s, OH-4c), 5.17 (1H, br s Hz, H-7c), 3.47 (1H, br s Hz, H-8c)[(g)], 5.85 (1H, d, *J*=2.2 Hz, H-12c)[(h)], 7.66 (1H, br s, OH-13c)[(i)], 5.52 (1H, d, *J*=2.2 Hz, H-14c)[(m)], 7.54 (2H, d, *J*=8.8 Hz, H-2d,6d)[(a)], 7.00 (2H, d, *J*=8.8 Hz, H-3d,5d)[(b)], 8.00 (1H, br s, OH-4d)[(J)], 5.66 (1H, d, *J*=10.2 Hz, H-7d)[(k)], 5.44 (1H, br d, *J*=10.2 Hz, H-8d)[(l)], 8.60 (1H, br s, OH-11d)[(c)], 6.38 (1H, d, *J*=2.2 Hz,

H-12d)[d], 6.31 (1H, d, J=2.2 Hz, H-14d)[f], 1.23 (3H, t, J=7.0 Hz, CH_3 in OEt-4b), 3.81 (2H, q, J=7.0 Hz, CH_2 in OEt-4b). [a]–[i]: overlapping. [j]–[m]: interchangeable.

*4.3.12. Methylation of **2** and **2a**.* (+)-Isohopeaphenol (**2**) (4 mg), previously isolated from the stem bark of *V. indica*,[1,2] was reacted with K_2CO_3 (200 mg) and MeI (10 mg) in dry acetone under reflux for 6 h. The reaction mixture was treated in the usual manner and the crude product (5 mg) obtained was purified by prep. TLC (*n*-hexane/EtOAc 1:1) to provide permethyl ether (**2c**) (4 mg). Monomethyl ether of (+)-isohopeaphenol (**2a**) (2 mg) was treated in the same manner as **2** to afford **2c** (2 mg).

*4.3.13. (+)-Isohopeaphenol permethyl ether (**2c**).* A pale yellow solid; $[\alpha]_D^{25}$ +312 (*c* 0.05, $CHCl_3$); Positive ion ESIMS *m*/*z*: 1069 $[M+Na]^+$; Positive ion HRESIMS *m*/*z*: 1069.4126 $[M+Na]^+$ (calcd 1069.4133 for $C_{66}H_{62}O_{12}Na$); ^1H NMR for **2a** [400 MHz, acetone-d_6] δ: 7.70 (2H, d, J=8.8 Hz, H-2a,6a), 7.17 (2H, d, J=8.8 Hz, H-3a,5a), 5.73 (1H, d, J=10.5 Hz, H-7a), 5.52 (1H, br d, J=10.5 Hz, H-8a), 6.55 (1H, d, J=2.4 Hz, H-12a), 6.36 (1H, d, J=2.4 Hz, H-14a), 6.41 (2H, d, J=8.6 Hz, H-2b,6b), 6.39 (2H, d, J=8.6 Hz, H-3b,5b), 5.04 (1H, br s, H-7b), 3.48 (1H, br s, H-8b), 5.98 (1H, d, J=2.2 Hz, H-12b), 5.54 (1H, d, J=2.2 Hz, H-14b), 6.41 (2H, d, J=8.6 Hz, H-2c,6c), 6.39 (2H, d, J=8.6 Hz, H-3c,5c), 5.04 (1H, br s, H-7c), 3.48 (1H, br s, H-8c), 5.98 (1H, d, J=2.2 Hz, H-12c), 5.54 (1H, d, J=2.2 Hz, H-14c), 7.70 (2H, d, J=8.8 Hz, H-2d,6d), 7.17 (2H, d, J=8.8 Hz, H-3d,5d), 5.73 (1H, d, J=10.5 Hz, H-7d), 5.52 (1H, br d, J=10.5 Hz, H-8d), 6.55 (1H, d, J=2.4 Hz, H-12d), 6.36 (1H, d, J=2.4 Hz, H-14d), 3.48 (3H, s, OMe), 3.48 (3H, s, OMe), 3.58 (3H, s, OMe), 3.58 (3H, s, OMe), 3.63 (3H, s, OMe), 3.63 (3H, s, OMe), 3.69 (3H, s, OMe), 3.69 (3H, s, OMe), 3.91 (3H, s, OMe), 3.91 (3H, s, OMe).

Supplementary data

1D NMR spectra (^1H, ^{13}C, and DEPT spectra) and 2D NMR spectra (^1H–^1H COSY, ^1H–^1H ROESY, ^1H–^{13}C HSQC, ^1H–^{13}C HMBC) for **1** at −20 °C in acetone-d_6. 1D NMR spectra for derivatives of **1**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.02.036. This data includes MOL file and InChiKeys of the most important compounds described in this article.

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