New Resveratrol Oligomers from the Stem Bark of *Hopea hainanensis*

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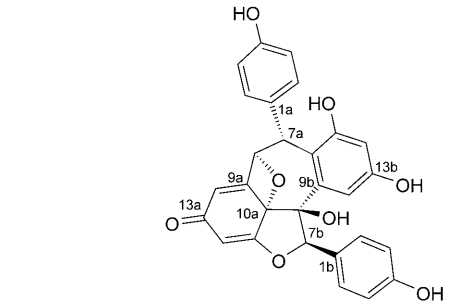
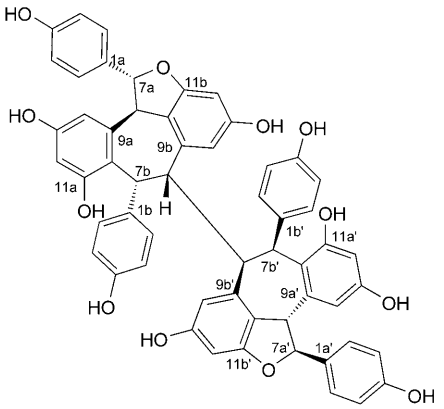
Three new resveratrol oligomers, hopeahainanphenol (**1**), neohopeaphenol A (**2**), and neoisohopeaphenol A (**3**), were isolated from the stem bark of *Hopea hainanensis* (Dipterocarpaceae). Their structures were elucidated by in-depth spectroscopic analyses, including 1D- and 2D-NMR techniques, and by HR-ESI-MS. All the three phytochemicals were tested *in vitro* for acetylcholinesterase (AChE) inhibitory and antitumor activity. The dimeric compound **2**, which corresponds to (1*S**,6*S**,7*S**,11b*S**)-1,6,7,11b-tetrahydro-1,7-bis(4-hydroxyphenyl)-6-[(1*R**,6*R**,7*R**,11b*R**)-1,6,7,11b-tetrahydro-4,8,10-trihydroxy-1,7-bis(4-hydroxyphenyl)benzo[6,7]cyclohepta-[1,2,3-*cd*]benzofuran-6-yl]benzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran-4,8,10-triol, was found to be significantly active against AChE, with an IC_{50} value of 7.66 ± 0.13 μM.

Introduction. – Resveratrol, a stilbene-based phytochemical, has been found to be substantially helpful for human health owing to its significant anticancer [1–5], antioxidative [5–8], anti-HIV [5], antimicrobial [5], and lung-microcirculation-improving actions [9]. Its oligomers have also received intense medicinal attention for their promising anticancer [10–12], antioxidant [11][13], and antifungal potentials [14]. Plants belonging to the Dipterocarpaceae family have been disclosed to be a rich source of stilbene oligomers [15–17]. The genus *Hopea*, which belongs to this family, comprises 90 species, most of which are distributed in Southeast Asia. *Hopea hainanensis*, endemic to Hainan island of China, has not been chemically investigated to date. In our continuous effort to search for structurally new and biologically active metabolites from plants [18] and specially harboring microbes [19–20], we have isolated from the MeOH extract of *Hopea hainanensis* stem bark three new compounds: the stilbene dimer hopeahainanphenol (**1**) and the two stilbene tetramers neohopeaphenol A (**2**) and neoisohopeaphenol A (**3**). We wish hereby to present the structural determination of these new phytochemicals.

Results and Discussion. – 1. *Structure Elucidation*. Hopeahainanphenol (**1**) was obtained as an optically active, brown, amorphous powder. Its molecular formula, $C_{28}H_{20}O_8$, with 19 degrees of unsaturation, was derived by HR-ESI-MS (negative mode) from the $[M-1]^-$ signal at 483.1099 ($C_{28}H_{19}O_8^-$; calc. 483.1080). This assumption was confirmed by a set of quasimolecular ion peaks at *m/z* 485 $[M+H]^+$ and 507 $[M+Na]^+$ in its positive-ion-mode ESI mass spectrum. The ^{13}C-NMR (DEPT) spectrum (*Table 1*) indicated 28 carbon resonances, and the HMQC spectrum showed 20 H-atoms, 15 of which were attached to C-atoms (three sp^3 and twelve sp^2 C-atoms). This indirectly suggested that five OH groups were present.



1



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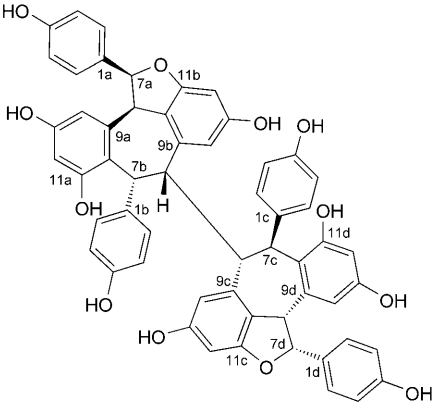

3

The presence of a cyclohexa-2,5-dien-1-one moiety was evidenced from the C(13a)[1]) carbonyl signal at δ(C) 186.49 [21], which showed clear HMBC correlations with H–C(12a) at δ(H) 5.51 and H–C(14a) at δ(H) 6.02, both being further correlated to C(10a) at δ(C) 62.62. One 1,2,3,5-tetra- and two 1,4-disubstituted benzene rings were indicated by a pair of *doublet*s ($J = 2.2$ Hz) at δ(H) 6.47/6.09, as well as two sets of mutually coupled two-proton *doublet*s ($J = 8.5$ Hz) at δ(H) 6.54/6.85 and 7.57/6.88. After subtracting 16 degrees of unsaturation due to the above four fragments, the remaining three degrees had to arise from three nonaromatic rings.

In the HMBC spectrum of **1** (*Fig. 1*), the discerned correlations of C(1a) with H–C(7a) and H–C(8a), and of C(7a) with H–C(2a,6a) established the connectivity of C(1a) to C(7a), which was further confirmed by an NOE correlation between H–C(7a) and H–C(2a,6a). The bond between C(7a) and C(8a) was inferred from the mutual HMBC correlations of the carbons with their neighboring H–C(8a) and H–C(7a) H-atoms, showing vicinal couplings to each other in the ^{1}H,^{1}H-COSY spectrum. Furthermore, the connection of C(8a) with C(9a) was indicated by the HMBC correlations of H–C(8a) with C(14a), as well as by the NOE correlation between H–C(8a) and H–C(14a). The connectivity of C(1b) with C(7b) was established by the HMBC correlations of H–C(2b,6b) with C(7b), and of H–C(7b) with C(1b) and C(2b,6b). The linkage between C(8b) and C(9b) was demonstrated by the HMBC correlation of H–C(14b) to C(8b). Moreover, C(7b) was connected with C(8b), as indicated by an HMBC correlation between H–C(7b) and C(9b). An OH group was at C(8b), as established by HMBC correlations of HO–C(8b) with C(1b), C(8b), C(9b), C(10b), and C(14b). Again, as highlighted in the HMBC spectrum of **1**, the connection of C(7a) with C(10b) was evidenced from the correlation of H–C(7a) with C(9b), C(10b), and C(11b), and that of H–C(8a) with C(10b). Furthermore, the magnitude of the chemical shifts of C(11a) (δ(C) 170.38) and C(7b) (δ(C) 87.21) and the HMBC correlation of H–C(7b) with C(11a) indicated an O-atom bridge between C(11a) and C(7b). The connectivity of C(10a) and C(8b) to form five- and seven-membered rings was established by the HMBC correlations of HO–C(8b) with C(9a) and C(10a). The remain-

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[1]) Arbitrary atom numbering. For systematic names, see *Exper. Part.*

Table 1. *^{1}H- and ^{13}C-NMR Data of* **1** *and* **2**. At 500 (^{1}H) and 125 MHz (^{13}C), in (D_6)DMSO (**1**) or (D_6)acetone (**2**); ^{1}H-NMR assignments based on HMBC experiments; δ in ppm, J in Hz.

Position	**1**			**2**		
	^{13}C	^{1}H	HMBC (H → C)	^{13}C	^{1}H	HMBC (H → C)
1a	129.95 (*s*)			130.80 (*s*)		
2a/6a	129.48 (*d*)	6.85 (*d*, *J* = 8.5)	1a, 6a/2a, 3a/5a, 4a, 7a	130.26 (*d*)	7.14 (br. *d*, *J* = 8.5)	1a, 6a/2a, 3a/5a, 4a, 7a
3a/5a	114.94 (*d*)	6.54 (*d*, *J* = 8.5)	1a, 2a/6a, 5a/3a, 4a, 7a	115.98 (*d*)	6.79 (br. *d*, *J* = 8.5)	1a, 2a/6a, 5a/3a, 4a
4a	155.88 (*s*)			159.09 (*s*)		
7a	47.47 (*d*)	5.98 (br. *s*)	1a, 2a/6a, 8a, 9a, 9b, 10b, 11b	88.35 (*d*)	5.77 (*d*, *J* = 12.0)	1a, 2a/6a, 8a, 9a, 11b
8a	71.12 (*d*)	4.53 (*t*, *J* = 1.7)	1a, 7a, 9a, 10a[a]), 14a, 10b	49.81 (*d*)	4.24 (*d*, *J* = 12.0)	1a, 7a, 9a, 10a, 13a, 14a, 9b, 10b, 11b, 12b, 14b
9a	150.22 (*s*)			142.38 (*s*)		
10a	62.62 (*s*)			121.01 (*s*)		
11a	170.38 (*s*)			158.76 (*s*)		
12a	102.42 (*d*)	5.51 (*d*, *J* = 1.0)	10a, 11a, 13a[a]), 14a	101.06 (*d*)	6.55 (*d*, *J* = 1.8)	10a, 11a, 13a, 14a
13a	186.49 (*s*)			158.54 (*s*)		
14a	129.31 (*d*)	6.02 (*t*, *J* = 1.7)	7a, 8a, 9a, 10a, 12a, 13a	106.24 (*d*)	6.31 (*d*, *J* = 1.8)	8a, 10a, 12a, 13a
1b	125.85 (*s*)			135.07 (*s*)		
2b/6b	131.50 (*d*)	7.57 (*d*, *J* = 8.5)	6b/2b, 3b/5b, 4b, 7b	129.28 (*d*)	6.91 (br. *d*, *J* = 8.5)	6b/2b, 3b/5b, 4b, 7b
3b/5b	116.12 (*d*)	6.88 (*d*, *J* = 8.5)	1b, 2b/6b, 5b/3b, 4b, 7b	115.14 (*d*)	6.57 (br. *d*, *J* = 8.5)	1b, 2b/6b, 5b/3b, 4b
4b	159.15 (*d*)			155.59 (*s*)		
7b	87.21 (*d*)	5.93 (*s*)	11a, 1b, 2b/6b, 9b, 14b	41.37 (*d*)	5.74 (br. *s*)	10a, 11a, 1b, 2b/6b, 8b, 9b
8b	74.16 (*s*)			48.21 (*d*)	3.98 (br. *s*)	10a, 1b, 9b, 10b, 14b, 8b′
9b	130.91 (*s*)			140.52 (*s*)		
10b	118.74 (*s*)			118.53 (*s*)		
11b	156.26 (*s*)			157.21 (*s*)		
12b	104.68 (*d*)	6.47 (*d*, *J* = 2.2)	10b,11b,13b,14b	95.11 (*d*)	5.74 (*d*, *J* = 2.0)	10b,11b,13b,14b
13b	156.61 (*s*)			157.02 (*s*)		
14b	110.10 (*d*)	6.09 (*d*, *J* = 2.2)	7b,8b,10b,12b,13b	111.18 (*d*)	5.14 (*d*, *J* = 2.0)	8b,12b,13b
4a-OH		9.06 (br. *s*)	2a/6a, 3a/5a, 4a			
4b-OH		9.82 (br. *s*)	2b/6b, 3b/5b, 4b			
8b-OH		6.01 (br. *s*)	9a, 10a, 1b, 8b, 9b, 10b, 14b			
11b-OH		9.71 (br. *s*)	10b, 11b, 12b			
13b-OH		9.40 (br. *s*)	9b, 12b, 13b, 14b			

[a]) Correlation peak observed in the HMBC spectrum recorded in (D_6)acetone, but not in (D_6)DMSO.

ing O-atom had to be between C(8a) and C(10a) to form a four-membered ring ether. This assumption was confirmed by the HMBC correlation of H–C(8a) with C(10a). Biosynthetically, the formulated structure of **1** was consistent with the biosynthetic pathways proposed for paucifloral C [15], hopeaphenol A [16], isohopeaphenol A [16], and vateraphenol B [17].

As to the relative configuration of **1**, the orientation of H–C(7a), which is *cis* to H–C(8a) and HO–C(8b), was established by the NOE correlation of H–C(7a) with H–C(8a) and HO–C(8b). This proposal was corroborated by the weak vicinal coupling (J = 1.7 Hz) between this pair of H-atoms. Finally, H–C(7b) was deduced to be *trans* to HO–C(8b) according to NOE correlations of H–C(7b) with H–C(14b), in accord with the absence of any NOE between H–C(7b) and HO–C(8b).

From the above data, the structure of hopeahainanphenol (**1**) was established as (1*R**,6*R**,7*R**,11b*S**,11c*R**)-1,6,7,11b-tetrahydro-8,10,11b-trihydroxy-1,7-bis(4-hydroxyphenyl)-6,11c-epoxybenzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran-4(4*H*)-one.

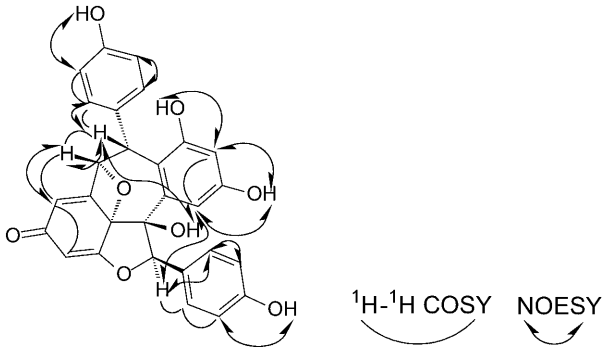

Fig. 1. *^{1}H,^{1}H-COSY and NOESY Correlations for* **1**

Neohopeaphenol A (**2**) was obtained as an optically inactive, yellowish, amorphous powder. Its molecular formula was disclosed to be $C_{56}H_{42}O_{12}$ by HR-ESI-MS, the quasimolecular ion being detected at *m/z* 907.2753 ($[M+H]^+$, $C_{56}H_{43}O_{12}^+$; calc. 907.2755). However, only 28 C-atoms were found by correlative inspections of its ^{1}H- and ^{13}C-NMR, DEPT, and HMQC spectra, suggesting that compound **2** was symmetric. Its ^{1}H- and ^{13}C-NMR spectra (*Table 1*) were similar to those of pauciflorol C [15], hopeaphenol A [16], isohopeaphenol A [16], and vateraphenol B [17], suggesting that compound **2** was one of the stereoisomers of these hopeaphenols, with the two units connected through a bond between C(8b) and C(8b′)[1]). This proposal was confirmed by combined analyses of its HMQC, HMBC, ^{1}H,^{1}H-COSY, and NOESY spectra (*Table 1* and *Fig. 2*, *a*).

The relative configuration of **2** was unambiguously elucidated by combined analyses of NOESY data and ^{1}H-NMR coupling constants. The dihydrobenzofuran ring was found to be *trans*-fused according to the coupling constant ($J=12.0$ Hz) of H–C(7a) and H–C(8a), NOE correlations between H–C(7a)/H–C(14a) and H–C(2a,6a)/H–C(8a), and the *absence* of an NOE between H–C(7a)/H–C(8a). The clear NOE correlation and the very weak coupling between H–C(7b) and H–C(8b) demonstrated that these two H-atoms were *cis* to each other. The orientation of H–C(8a), which is *trans* to H–C(7b), was disclosed by the NOE correlation of H–C(8a) and H–C(2b). There was no NOE between the pairs H–C(8a)/H–C(7b) and H–C(8a)/H–C(8b), in contrast to pauciflorol C [15]. Finally, H–C(8b′) was proposed to be *trans* to H–C(8b) by taking the advantage of its symmetrical nature, although the relative configuration of H–C(8b′) and H–C(8b) could not be assigned from the NOESY spectrum.

From the above data, compound **2**, which was named neohopeaphenol A, was determined as (1*S**,6*S**,7*S**,11b*S**)-1,6,7,11b-tetrahydro-1,7-bis(4-hydroxyphenyl)-6-[(1*R**,6*R**,7*R**,11b*R**)-1,6,7,11b-tetrahydro-4,8,10-trihydroxy-1,7-bis(4-hydroxyphenyl)benzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran-6-yl]benzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran-4,8,10-triol.

Neoisohopeaphenol (**3**) was obtained as an optically active, yellowish, amorphous powder. It had the same molecular formula as compound **2**, based on its HR-ESI mass spectrum, with *m/z* 907.2759 ($[M+H]^+$, $C_{56}H_{43}O_{12}^+$; calc. 907.2755). This suggestion was in accordance with 56 C-atoms found by correlated inspections of its ^{1}H- and ^{13}C-NMR, DEPT, and HMQC spectra. Its ^{1}H- and ^{13}C-NMR spectra (*Table 2*) were similar to those of pauciflorol C [15], hopeaphenol A [16], isohopeaphenol A

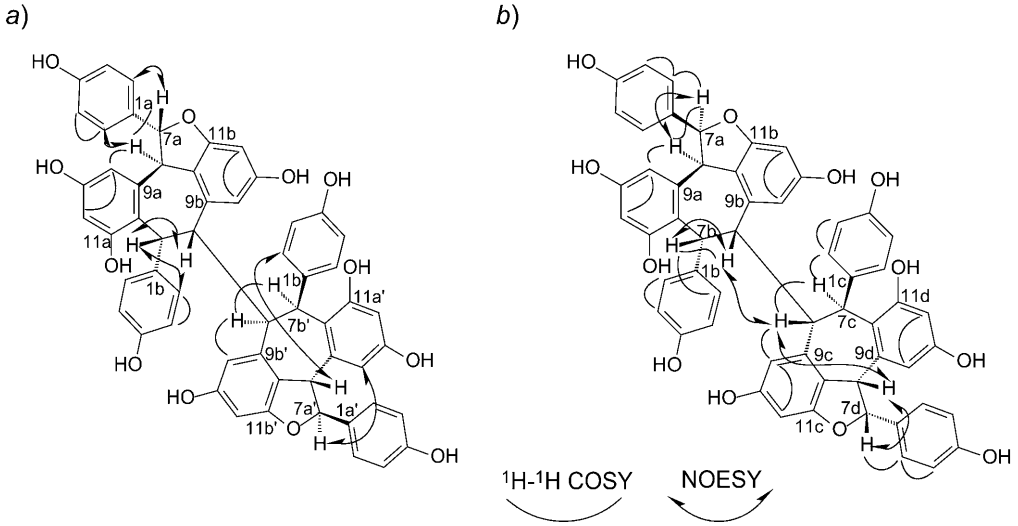

Fig. 2. *^{1}H,^{1}H-COSY and NOESY Correlations for* **2** (a) *and* **3** (b)

[16] and vateraphenol B [17], suggesting that compound **3** was a stereoisomer of these hopeaphenols. This proposal was further confirmed by combined analyses of its HMQC, HMBC, and ^{1}H,^{1}H-COSY spectra (*Table 2* and *Fig. 2*, *b*).

The relative configuration of **3** was established by combined analyses of NOESY data and ^{1}H-NMR coupling constants. The two dihydrobenzofuran rings were *cis*-fused according to NOE correlations between the pairs H–C(7a)/H–C(8a) and H–C(7d)/H–C(8d). The orientations of H–C(7b), H–C(8b), H–C(8c), and H–C(8d) were deduced from the clear NOE correlations between the pairs of H–C(7b)/H–C(8b), H–C(8b)/H–C(8c), and H–C(8c)/H–C(8d) in the NOESY spectrum [15]. H–C(7b) and H–C(7c) were shown to be *trans* to H–C(8a) and H–C(8c), respectively, as inferred from the *absence* of NOE correlations between the pairs H–C(8a)/H–C(7b) and H–C(7c)/H–C(8c). To rationalize the discerned NOE effects, particularly that between H–C(8b) and H–C(8c), a 3D structure of **3** (*Fig. 3*) was generated with the Chem3D (version 8.0) software, using the MM2 force field for energy minimization. The calculated distances between H–C(7a)/H–C(8a) (2.302 Å), H–C(7b)/H–C(8b) (2.510 Å), H–C(7d)/H–C(8d) (2.990 Å), and H–C(8b)/H–C(8c) (2.474 Å) were all below 3 Å, well-consistent with the detected strong NOE correlations between each of these H-atom pairs. Also, the allocated orientations of H–C(8b) and H–C(8c) were in accord with the calculated dihedral angle (56.40°) for H–C(8b)–C(8c)–H.

From the above data, the structure of neoisohopeaphenol (**3**) was identified as (1*S**,6*R**,7*R**,11b*R**)-1,6,7,11b-tetrahydro-1,7-bis(4-hydroxyphenyl)-6-[(1*R**,6*R**,7*S**,11b*S**)-1,6,7,11b-tetrahydro-4,8,10-trihydroxy-1,7-bis(4-hydroxyphenyl)benzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran-6-yl]benzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran-4,8,10-triol.

2. *Bioassay.* The polyphenols **1**–**3** were assessed *in vitro* for antitumor activity and inhibition on acetylcholinesterase (AChE), the latter being closely associated with *Alzheimer*'s disease (AD) [22][23]. Neohopeaphenol (**2**) was found to be significantly

Table 2. *^{1}H- and ^{13}C-NMR Data of* **3**. At 500 (^{1}H) and 125 MHz (^{13}C) in (D_6)acetone; ^{1}H-NMR assignments based on HMBC experiments; δ in ppm, J in Hz.

Position	^{13}C	^{1}H	HMBC (H → C)	Position	^{13}C	^{1}H	HMBC (H → C)
1a	134.28 (*s*)			1c	133.38 (*s*)		
2a/6a	128.34 (*d*)	7.16 (*d*, *J* = 8.5)	6a/2a, 3a/5a, 4a, 7a	2c/6c	130.55 (*d*)	7.13 (*d*, *J* = 8.5)	6c/2c, 3c/5c, 4c, 7c
3a/5a	115.92 (*d*)	6.77 (*d*, *J* = 8.5)	1a,5a/3a, 4a	3c/5c	115.32 (*d*)	6.67 (*d*, *J* = 8.5)	1c, 2c, 5c/3c, 4c
4a	158.02 (*s*)			4c	155.74 (*s*)		
7a	94.72 (*d*)	5.31 (*d*, *J* = 5.3)	1a, 2a/6a, 8a, 9a, 10a, 14a, 11b	7c	36.96 (*d*)	5.15 (*d*, *J* = 3.4)	7b, 1c, 9c, 9d, 10d, 11d
8a	57.36 (*d*)	4.65 (*d*, *J* = 5.2)	1a, 7a, 9a, 10a, 13a, 14a, 9b, 11b	8c	49.25 (*d*)	4.51 (*d*, *J* = 10.7)	8b, 1c, 9c, 10c, 11c, 13c, 14c
9a	147.92 (*s*)			9c	141.70 (*s*)		
10a	123.27 (*s*)			10c	122.09 (*s*)		
11a	154.88 (*s*)			11c	155.82 (*s*)		
12a	107.35 (*d*)	6.06 (br. *s*)	10a, 11a, 14a	12c	95.46 (*d*)	6.09 (br. *s*)	11c, 13c, 14c
13a	159.20 (*s*)			13c	158.62 (*s*)		
14a	106.91 (*d*)	6.42 (*d*, *J* = 1.6)	8a, 10a, 12a, 13a	14c	105.43 (*d*)	6.09 (br. *s*)	9c, 12c, 13c
1b	131.32 (*s*)			1d	130.61 (*s*)		
2b/6b	129.20 (*d*)	6.37 (*d*, *J* = 8.2)	6b/2b,3b,4b,7b	2d/6d	130.06 (*d*)	7.20 (*d*, *J* = 8.5)	6d/2d, 3d/5d, 4d
3b/5b	115.74 (*d*)	6.49 (*d*, *J* = 8.4)	1b, 5b/3b, 4b	3d/5d	115.92 (*d*)	6.75 (*d*, *J* = 8.6)	1d, 5d/3d, 4d
4b	155.82 (*s*)			4d	158.54 (*s*)		
7b	53.01 (*d*)	3.09 (*d*, *J* = 11.3)	1b, 8b, 9b, 7c	7d	90.38 (*d*)	5.74 (*d*, *J* = 11.7)	11c, 2d, 8d, 9d
8b	57.64 (*d*)	4.07 (*t*, *J* = 11.1)	7c, 8c	8d	48.89 (*d*)	4.40 (*d*, *J* = 11.6)	1d, 7d, 10d, 14d
9b	141.60 (*s*)			9d	143.18 (*s*)		
10b	122.09 (*s*)			10d	124.24 (*s*)		
11b	161.41 (*s*)			11d	156.59 (*s*)		
12b	96.25 (*d*)	6.16 (*d*, *J* = 1.6)	10b, 11b, 13b, 14b	12d	96.34 (*d*)	6.06 (br. *s*)	10d, 11d, 13d, 14d
13b	159.60 (*s*)			13d	156.10 (*s*)		
14b	101.95 (*s*)	6.28 (*t*, *J* = 1.8)	10b, 12b, 13b	14d	101.41 (*d*)	6.27 (*d*, *J* = 1.9)	10d, 12d, 13d

active against AChE, with an IC_{50} value[2]) of 7.66 ± 0.13 μM, relative to 2.04 ± 0.13 μM in the case of tacrine (positive control). To our knowledge, compound **2** is the first resveratrol oligomer that inhibits AChE. Compounds **1** and **3** were not active towards AChE. Also, regarding antitumor activities, none of the three polyphenols was active against the KB, BEL7402, SW1116, and Hela cell lines. Our results contrast previous communications, in which similar types of phytochemicals were reported to possess antitumor activities [10–12].

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[2]) Inhibition concentration lowering the activity of the enzyme by 50%.

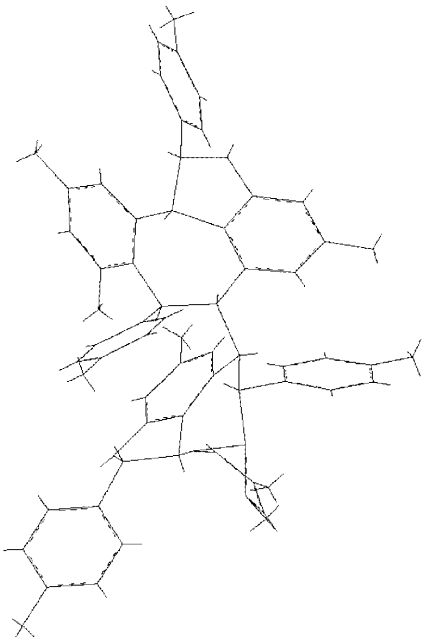

Fig. 3. *Calculated three-dimensional structure of* **3**

Experimental Part

General. Silica gel (200–300 mesh) for column chromatography (CC) was purchased from *Qingdao Marine Chemical Factory* (Qingdao, China), *ODS* silica gel was from *Nacalai Tesque* (Kyoto, Japan), and *Sephadex LH-20* gel was from *Pharmacia Biotech* (Sweden). Melting points (m.p.) were determined on a *Boetius* micro-melting-point apparatus; uncorrected. IR Spectra: in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker DRX-500* spectrometer, at 500 (^1H) and 125 MHz (^{13}C), resp.; chemical shifts δ in ppm rel. to Me_4Si, coupling constants J in Hz. HR-ESI-MS: *Mariner System 5304* instrument; in m/z.

Plant Material. The stems and twigs of *Hope hainanensis* were collected in July 2003 from the Botanical Garden of South China University of Tropical Agriculture, Hainan province, P. R. China. The specimen was identified by Prof. *X. Q. Zheng* (South China University of Tropical Agriculture, Haikou, China).

Extraction and Isolation. The peeled bark of *Hope hainanensis* was dried and chopped. The MeOH extract of the bark shreds was concentrated *in vacuo* to give a brown residue, which was subsequently chromatographed (SiO_2; $CHCl_3$/MeOH gradients of increasing polarity): eight fractions (Fr.). *Fr. 3*, eluted with $CHCl_3$/MeOH 10 : 1, was further purified by repeated gel filtration (*Sephadex LH-20*; MeOH) to afford **1** (15 mg). *Fr. 4*, eluted with $CHCl_3$/MeOH 5 : 1, was also repeatedly purified by gel filtration *(Sephadex LH-20*; MeOH) to afford **2** (13 mg) and **3** (10 mg).

Hopeahainanphenol (=*(1*R*,6*R*,7*R*,11b*S*,11c*R*)-1,6,7,11b-Tetrahydro-8,10,11b-trihydroxy-1,7-bis(4-hydroxyphenyl)-6,11c-epoxybenzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran-4(4*H*)-one*; **1**). Brown, amorphous powder. M.p. 138.5–139.8°. $[\alpha]_D^{20} = +50.6$ ($c = 1$ mg/ml, MeOH). IR (KBr): 3249.2, 3070.6, 3017.0, 2912.9, 1669.3, 1616.1, 1625.9, 1584.9, 1518.1, 1451.6, 1371.9, 1170.0, 852.1, 802.9. ^1H- and ^{13}C-NMR: see *Table 1*. ESI-MS: 507 ($[M+Na]^+$), 485 ($[M+H]^+$). HR-ESI-MS (neg. mode): 483.1099 ($[M-H]^-$, $C_{28}H_{19}O_8^-$; calc. 483.1080).

Neohopeaphenol A (=*(1*S*,6*S*,7*S*,11b*S*)-1,6,7,11b-Tetrahydro-1,7-bis(4-hydroxyphenyl)-6-[(1*R*,6*R*,7*R*,11b*R*)-1,6,7,11b-tetrahydro-4,8,10-trihydroxy-1,7-bis(4-hydroxyphenyl)benzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran-6-yl]benzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran-4,8,10-triol*; **2**). Yellowish, amorphous powder. M.p. 146.0–147.0°. $[\alpha]_D^{20} = 0$ ($c = 0.4$ mg/ml, MeOH). IR (KBr): 3214.7, 1611.9, 1597.2, 1512.4, 1442.3, 1342.8, 1233.8, 1173.9, 993.8, 837.1. ^1H- and ^{13}C-NMR: see *Table 1*. ESI-MS: 1834.9 [$2M+Na]^+$, 929.2 ($[M+Na]^+$, 907.1 ($[M+H]^+$). HR-ESI-MS: 907.2753 ($[M+H]^+$, $C_{56}H_{43}O_{12}^+$; calc. 907.2755) .

Neoisohopeaphenol A (=*(1*S*,6*R*,7*R*,11b*R*)-1,6,7,11b-Tetrahydro-1,7-bis(4-hydroxyphenyl)-6-[(1*R*,6*R*,7*S*,11b*S*)-1,6,7,11b-tetrahydro-4,8,10-trihydroxy-1,7-bis(4-hydroxyphenyl)benzo[6,7]cyclohepta[1,2,3-*cd*]-

*benzofuran-6-yl]benzo[6,7]cyclohepta[1,2,3-*cd*]benzofuran-4,8,10-triol*; **3**).Yellowish, amorphous powder. M.p. 98.3–99.2°. $[\alpha]_D^{20} = +170$ ($c = 0.2$ mg/ml, MeOH). IR (KBr): 3409.7, 1719.9, 1659.8, 1608.7, 1515.3, 1460.4, 1335.1, 1158.6, 1110.3, 1084.5, 998.0, 840.7. ^{1}H- and ^{13}C-NMR: see *Table 2*. ESI-MS: 1835.0 $[2M+Na]^+$, 929.3 $[M+Na]^+$, 907.2 $[M+H]^+$. HR-ESI-MS: 907.2759 ($[M+H]^+$, $C_{56}H_{43}O_{12}^+$; calc. 907.2755).

Acetylcholinesterase (AChE) *Inhibition.* The enzyme activity was evaluated spectrophotometrically by a modified method of *Ellman* [24][25]. Briefly, 130 µl of 0.1M aq. phosphate buffer (pH 8.0), 20 µl of 0.333 mM 5,5′-dithiobis[2-nitrobenzoicacid] (DTNB), 10 µl of test-compound (or control) soln. in MeOH, and 20 µl of AChE soln. (0.08 units/l) were mixed and incubated for 15 min at 25°. The reaction was then initiated by addition of 20 µl of acetylthiocholine iodide (0.53 mM), and the absorbance at 412 nm was measured. All assays were performed at least at ten different concentrations, and each run was performed in triplicate, before IC_{50} values were calculated. Tacrine was co-assayed as a positive control at appropriate concentrations.

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