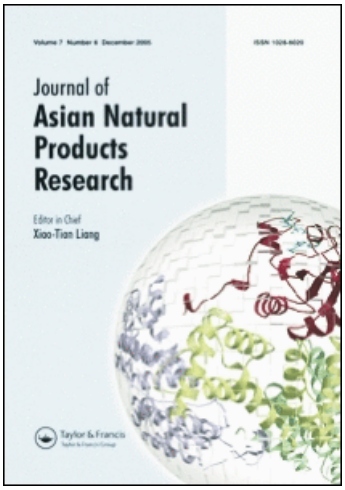

Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

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To cite this Article Wang, Ying-Hong , Huang, Kai-Sheng and Lin, Mao(2001) 'Four New Stilbene Dimers from the Lianas of *Gnetum Hainanense*', Journal of Asian Natural Products Research, 3: 3, 169 — 176
To link to this Article: DOI: 10.1080/10286020108041387
URL: http://dx.doi.org/10.1080/10286020108041387

JANPR, Vol. 3, pp. 169–176
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FOUR NEW STILBENE DIMERS FROM THE LIANAS OF *GNETUM HAINANENSE*

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(Received 13 June 2000; In final form 15 June 2000)

Four new stilbene dimers, gnetuhainins P (**1**), Q (**2**), K (**3**) and L (**4**), were isolated from the lianas of *Gnetum hainanense* C. Y. Cheng. Their structures and relative configurations were determined on the basis of spectroscopic evidence, especially 2D NMR techniques.

Keywords: *Gnetum hainanense*; Gnetaceae; Gnetuhainins P, Q, K, L; Stilbene dimers

INTRODUCTION

In the previous papers [1,2], different structural types of stilbene dimers have been isolated from the lianas of *Gnetum hainanense*. Continuous investigation on the stilbenoids from the same resource resulted in the isolation of four new stilbene dimers, named gnetuhainins P (**1**), Q (**2**), K (**3**) and L (**4**). Compound **2** is the first mixed dimer from an isorhapotigenin unit and a resveratrol unit, compound **3** is the first mixed dimer of isorhapotigenin and gnetol. Here we report the isolation and structural elucidation of **1**–**4**.

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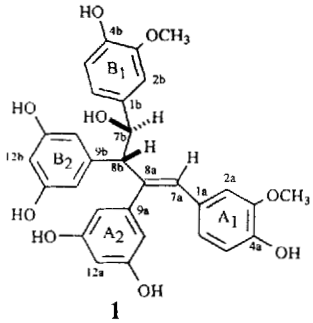

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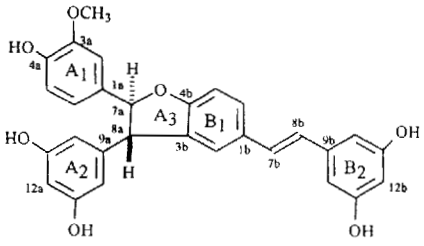

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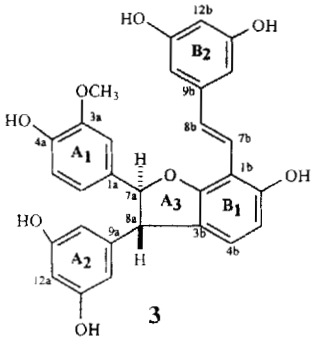

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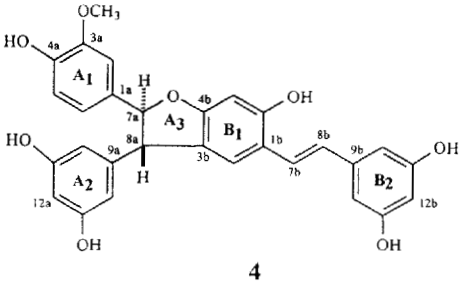

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RESULTS AND DISCUSSION

Gnetuhainin P (**1**) was obtained as a yellowish amorphous powder, $[\alpha]_D^{25}$ + 6.6 (*c* 0.092, MeOH). The high resolution FABMS *m/z* 533.1866 $[M+H]^+$ gave a molecular formula of $C_{30}H_{28}O_9$ ($C_{30}H_{29}O_9$ requires 533.1812), which corresponds to an isorhapontigenin dimer. The ^1H NMR spectrum presented two sets of ABX system signals at δ 6.45 (1 H, *d*, $J = 2.1$ Hz), 6.62 (1 H, *d*, $J = 8.4$ Hz), 6.65 (1 H, *dd*, $J = 8.4$, 2.1 Hz), and δ 6.84 (1 H, *d*, $J = 2.1$ Hz), 6.61 (1 H, *d*, $J = 8.4$ Hz), 6.74 (1 H, *dd*, $J = 8.4$, 2.1 Hz) for rings A_1 and B_1; two sets of AB_2 system signals at δ 6.08 (2 H, *d*, $J = 2.1$ Hz), 6.24 (1 H, *t*, $J = 2.1$ Hz), and δ 6.06 (2 H, *d*, $J = 2.1$ Hz), 6.03 (1 H, *t*, $J = 2.1$ Hz) for ring A_2 and B_2, two coupled doublets at δ 5.05 (1 H, *d*, $J = 9.9$ Hz) and 3.70 (1 H, *d*, $J = 9.9$ Hz) for two methine protons, a singlet at δ 6.77 for an olefinic proton and two singlets at δ 3.46 and 3.70 for the methoxy groups. The ^{13}C NMR spectrum showed signals for 26 olefinic and aromatic carbons, and four aliphatic carbons, including one methine carbon attached to a hydroxy group at δ 75.7. All protonated carbons were confirmed by

HMQC spectrum. The HMBC spectrum (Fig. 1a) showed CH long-range correlations between H-7a/C-2a, 6a, 8b, H-10(14)a/C-8a, H-8b/C-7a, 7b, 9b, 10(14)b, H-7b/C-8a, 2b, 6b, which suggested that compound **1** was formed from two isorhapontigenin units with a linkage between C-8a and C-8b. The connectivity was different from that of gnetifolin O [3], an isorhapontigenin dimer isolated by our research group from *Gnetum montanum*. The stereochemistry of **1** was determined on the basis of NOE interactions in the NOESY spectrum (Fig. 1b). The NOEs between H-7a/H-8b, H-7a/H-7b indicated a *cis* orientation of ring A_1 and A_2. The NOEs between H-8b/H-2b, 6b, H-7b/H-10(14)b suggested that H-7b and H-8b were *trans* orientated, this was supported by the large coupling constant between these two protons. Thus the stereochemistry was determined to be as shown in **1**.

Gnetuhainin Q (**2**) was obtained as a pale white amorphous powder. The high resolution FABMS *m/z* 485.1517 $[M+H]^+$ was in agreement with a molecular formula of $C_{29}H_{24}O_7$ ($C_{29}H_{25}O_7$ requires 485.1600), which along with its ^1H and ^{13}C NMR spectra indicated that **2** was dimeric with a resveratrol unit and an isorhapontigenin unit. The ^1H NMR spectrum showed two sets of signals for two AB_2 system protons on rings A_2 and B_2 at δ 6.19 (2H) and 6.27, 6.52 (2H) and 6.24; two sets of ABX systems signals for rings A_1 and B_1 at δ 7.02, 6.82, 6.84, and δ 7.24, 7.42, 6.81; two doublets for two *trans* olefinic protons at δ 7.05 and 6.91; two doublets for two aliphatic protons on the dihydrobenzofuran moiety at δ 5.42, 4.50 and a singlet at δ 3.82 (3H) for the methoxy group. There were no AA′BB′ system signals of the 4-hydroxybenzene group in the resveratrol unit in the ^1H

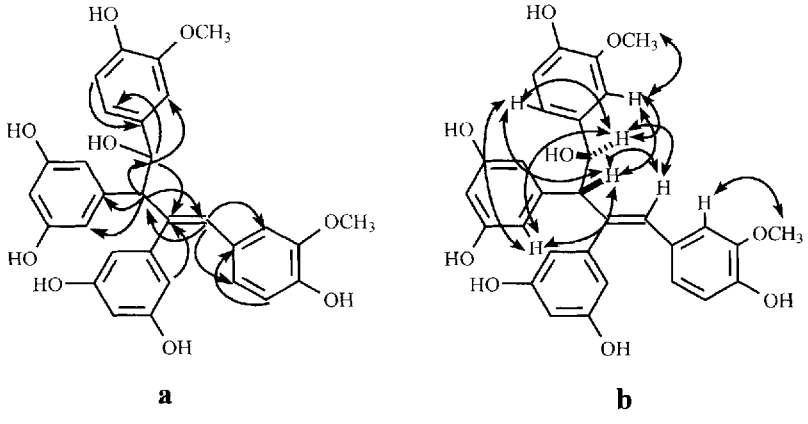

FIGURE 1 CH long-range correlations from the HMBC spectrum (a) and NOE interactions from the NOESY spectrum (b) of **1**.

NMR spectrum. This indicated that **2** was dimerized from a resveratrol unit and an isorhapontigenin unit through formation of a dihydrobenzofuran moiety on ring B_1. The CH long-range correlations in the HMBC spectrum (Fig. 2a) confirmed the supposition regarding the planar structure of **2**. The *trans* relationship between H-7a and H-8a was deduced from the strong NOE enhancements between H-7a/H-10(14)a and between H-8a/H-2a, 6a in the NOESY spectrum (Fig. 2b). Thus, the configurations at C-7a and C-8a were determined to be rel-(7aS, 8aS), as shown in structure **2**.

Gnetuhainins K(**3**) and L(**4**) were obtained as a mixture in the proportion of *ca.* 1:1, and were not separated by HPLC. The high resolution ESIMS *m/z* 501.1557 $[M+H]^+$ gave a molecular formula of $C_{29}H_{24}O_8$ for **3** and **4** ($C_{29}H_{25}O_8$ requires 501.1549). The ^1H NMR spectrum of **3** (analyzed as a mixture with **4**, with the aid of ^1H ^1H COSY, HMQC, HMBC and NOESY spectra) exhibited the signals for an isorhapotigenin unit at δ 6.98 (1H, *d*, $J=2.1$ Hz), 6.76 (1H, *d*, $J=8.4$ Hz) and 6.64 (1H, *dd*, $J=8.4$, 2.1 Hz) for an ABX system of ring A_1; δ 6.15 (2H, *d*, $J=2.1$ Hz) and 6.17 (1H, *t*, $J=2.1$ Hz) for an AB_2 system of ring A_2; δ 5.48 (1H, *d*, $J=7.5$ Hz) and 4.28

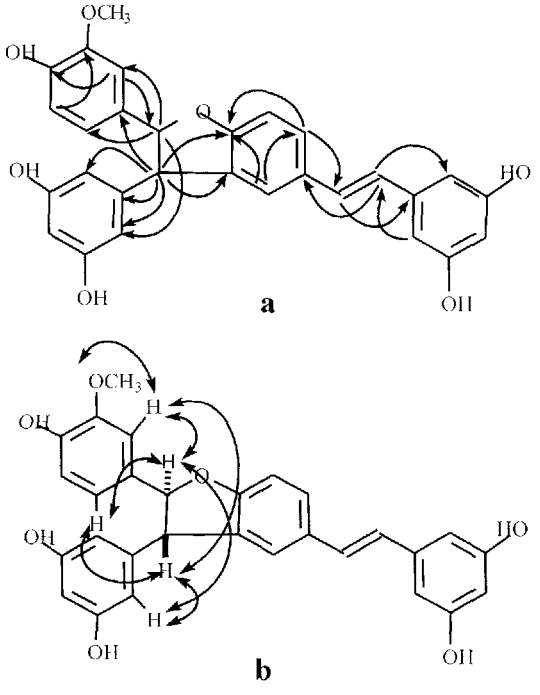

FIGURE 2 CH long-range correlations from the HMBC spectrum (a) and NOE interactions from the NOESY spectrum (b) of **2**.

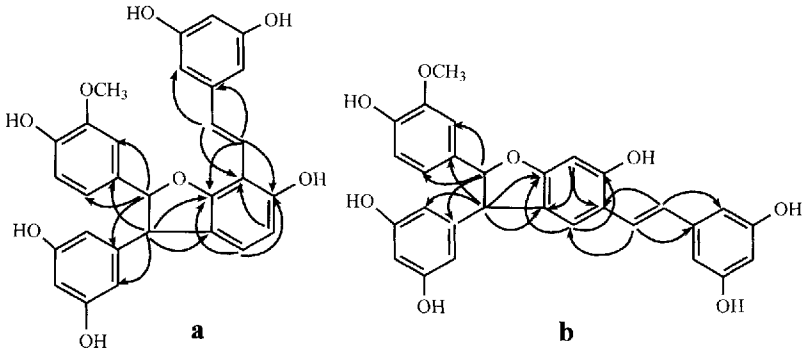

FIGURE 3 CH long-range correlations from their HMBC spectra for compounds **3** (a) and **4** (b).

(1H, *d*, $J = 7.5$ Hz) for two *ortho*-coupled protons of a dihydrofuran group and δ 3.75 (3H, *s*) for methoxy group and the signals for a gnetol unit at δ 6.62 (1H, *d*, $J = 8.7$ Hz) and 6.34 (1H, *d*, $J = 8.7$ Hz) for ring B_1; δ 6.43 (2H, *d*, $J = 2.1$ Hz) and 6.20 (1H, *t*, $J = 2.1$ Hz) of an AB_2 system of ring B_2, and δ 7.34 (1H, *d*, $J = 16.5$ Hz) and 7.48 (1H, *d*, $J = 16.5$ Hz) of two *trans* olefinic protons, which were characteristic signals of gnetol because of their downfield-shift. Since H-4b and H-5b on ring B_1 showed two *ortho*-coupled doublets, we concluded that an isorhapotigenin unit and a gnetol unit were connected in a dihydrobenzofuran moiety at C-2b, 3b, 7a and 8a, which was confirmed by long-range cross-peaks in the HMBC spectrum (Fig. 3a). The *trans* relationship between H-7a and H-8a was determined by NOE enhancements between H-7a/H-10(14)a and between H-8a/H-2(6)a observed in the NOESY spectrum, and **3** therefore had configuration of *rel*-(7a*S*, 8a*S*). The remaining signals in the spectrum of the mixture of **3** and **4** were attributable to compound **4**, which along with its ^{13}C NMR data (see Tab. II) indicated that it was dimeric with an isorhapotigenin unit and an oxyresveratrol unit. The connectivities of **4** were confirmed by long-range correlations in HMBC spectrum (Fig. 3b), and the relative configuration of *rel*-(7a*S*, 8a*S*) for **4** was established by NOE enhancements between H-7a/H-10(14)a and between H-8a/H-2(6)a in the NOESY spectrum.

EXPERIMENTAL SECTION

General Experimental Procedures

Optical rotations were determined on a Perkin-Elmer digital polarimeter. UV spectra were recorded on a Shimadzu UV-300 spectrophotometer. IR

spectra were recorded on a Perkin-Elmer 683 infrared spectrometer in KBr pellet. NMR spectra were carried out on Varian Mercury-300 NMR spectrometer using TMS as internal standard. EIMS and FABMS were taken on an Autospec-Ulma-Tof mass spectrometer. HPLC was performed on a Waters 411 instrument equipped with an UV detector.

Plant Material

The lianas of *G. hainanense* C. Y. Cheng (Gnetaceae) were collected at Jianfengling in Ledong County of Hainan Province, China in September 1991, identified by Prof. W.-Z. Song, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College. A voucher specimen (No. 910920) has been deposited in the herbarium of this institute.

Extraction and Isolation

The dried and powdered lianas of *G. hainanense* (22 kg) were extracted with 95% EtOH by refluxing, and the crude extract (1.9 kg) obtained after removing solvent *in vacuo* was further extracted with EtOAc to provide 500 g of residue. It was subjected to a silica gel column (100–200 mesh, 10 × 150 cm) eluted with $CHCl_3$–MeOH increasing MeOH gradually to provided seven fractions (A–G). Fraction E (81.7 g) was subjected to a silica gel column (100–200 mesh, 5 × 100 cm) eluted with cyclohexane–acetone (1:1) to afford fractions E_1–E_5. Fraction E_5 was subjected to medium-pressure liquid chromatography (Lobar column, RP-18, 43–63 μm, 2.5 × 31 cm, MeOH–H_2O of 3:7) to afford **1** (28 mg). Treatment of fraction E_1 using the same methods as for fraction E_5 yielded **2** (12 mg), a mixture of **3** and **4** (20 mg).

Gnetuhainin P (**1**): Yellowish amorphous powder, $[\alpha]_D^{25}$ + 6.6(*c* 0.092, MeOH). UV (MeOH) λ_{max} (log ε) 272 (4.3) nm; IR (KBr) ν_{max} 3307, 1695, 1604, 1516, 1452, 1277, 1155, 1001, 845 and 818 cm^{-1}; ^1H (300 MHz) and ^{13}C (75 MHz) NMR data, see Table I; The high resolution FABMS *m/z* 533.1866 $[M+H]^+$ (calcd for $C_{30}H_{29}O_9$, 533.1812).

Gnetuhainin Q (**2**): Pale white amorphous powder; UV (MeOH) λ_{max} 282 (sh), 305, 324 (sh) nm; IR (KBr) ν_{max} 3375, 1697, 1603, 1515, 1487, 1452, 1345, 1271, 1234, 1152, 996, 960 and 833 cm^{-1}; ^1H (300 MHz) and ^{13}C (75 MHz) NMR data, see Table I; The high resolution FABMS *m/z* 485.1571 $[M+H]^+$ (calcd for $C_{39}H_{24}O_7$, 485.1600).

TABLE I ^{1}H and ^{13}C NMR Data for Compounds **1** and **2**[a]

	1		**2**	
Position	^{1}H	^{13}C	^{1}H	^{13}C
1a		130.3		132.7
2a	6.45 d (2.1)	112.6	7.02 d (2.1)	110.9
3a		147.4		148.3
4a		146.0		147.4
5a	6.62 d (8.4)	115.0	6.84 overlap	115.5
6a	6.65 dd (8.4, 2.1)	123.7	6.82 overlap	120.1
7a	6.77 s	127.9	5.42 d (8.4)	94.2
8a		141.6	4.50 d (8.4)	57.7
9a		144.9		144.9
10(14)a	6.08 d (2.1)	108.7	6.19 d (2.1)	107.3
11(13)a		159.4		159.6[b]
12a	6.24 t (2.1)	101.8	6.27 t (2.1)	102.5[c]
OMe-3a	3.46 s	55.3	3.82 s	56.2
1b		136.3		131.6
2b	6.84 d (2.1)	111.7	7.24 br s	123.8
3b		147.4		132.1
4b		146.0		160.5
5b	6.61 d (8.4)	114.8	6.81 d (8.1)	110.6
6b	6.74 dd (8.4, 2.1)	120.6	7.42 dd (8.1, 1.8)	128.5
7b	5.05 d (9.9)	75.7	7.05 d (15.9)	129.0
8b	3.70 d (9.9)	64.7	6.91 d (15.9)	127.1
9b		143.8		140.6
10(14)b	6.06 d (2.1)	108.4	6.52 d (2.1)	105.5
11(13)b		158.4		159.4[b]
12b	6.03 t (2.1)	101.3	6.24 t (2.1)	102.2[c]
OMe-3b	3.70 s	56.0		

[a]Measured in CD_3COCD_3 at 300 MHz for ^{1}H and 75 MHz for ^{13}C respectively, with assignments confirmed by ^{1}H-^{1}H COSY, HMQC, HMBC and NOESY spectra.
[b,c]May be interchanged within the same column.

TABLE II ^{1}H and ^{13}C NMR data for compounds **3** and **4**[a]

	3		**4**	
Position	^{1}H	^{13}C	^{1}H	^{13}C
1a		132.5		132.1
2a	6.98 d (2.1)	109.7	6.93 d (2.1)	109.9
3a		147.7		147.7
4a		146.7		146.9
5a	6.76 d (8.4)	114.8	6.76 d (8.4)	114.9
6a	6.64 dd (8.4, 2.1)	118.8	6.75 dd (8.4, 2.1)	119.1
7a	5.48 d (7.5)	93.4	5.34 d (7.8)	93.7
8a	4.28 d (7.5)	56.6	4.31 d (7.8)	56.6
9a		144.9		144.7
10a	6.15 d (2.1)	106.4	6.16 d (2.1)	106.4
11a		158.6		158.7
12a	6.17 t (2.1)	101.4	6.15 t (2.1)	101.3
13a		158.6		158.7
14a	6.15 d (2.1)	106.4	6.16 d (2.1)	106.4
1b		108.6		117.2
2b		158.6	7.13 s	122.2

TABLE II (Continued)

	3		4	
Position	^1H	^{13}C	^1H	^{13}C
3b		121.7		122.2
4b	6.62 d (8.7)	123.9		160.4
5b	6.34 d (8.7)	108.0	6.44 s	96.9
6b		155.8		156.0
7b	7.34 d (16.5)	119.8	7.30 d (16.5)	123.4
8b	7.48 d (16.5)	131.3	6.78 d (16.5)	125.4
9b		141.0		140.5
10b	6.43 d (2.1)	104.5	6.44 d (2.1)	104.5
11b		158.8		158.8
12b	6.20 t (2.1)	101.7	6.21 t (2.1)	101.8
13b		158.8		158.8
14b	6.43 d (2.1)	104.5	6.44 d (2.1)	104.5
OMe-3a	3.75 s	55.5	3.75 s	55.5

[a]Measured in CD_3COCD_3 at 300 MHz for ^1H and 75 MHz for ^{13}C respectively, with assignments confirmed by ^1H-^1H COSY, HMQC, HMBC and NOESY spectra.

Gnetuhainins K (**3**) *and L* (**4**): Off-white amorphous powder as a mixture of **3** and **4**; ^1H (300 MHz) and ^{13}C (75 MHz) NMR data, see Table II; HRESI-MS *m/z* 501.1557 $[MH]^+$ (calcd for $C_{29}H_{25}O_8$, 501.1549).

Acknowledgments

This research program was supported by the National Natural Science Foundation of China (No. 39570836). The authors thank the Department of Instrumental Analysis, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, for the measurement of UV, IR, and MS spectra.

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