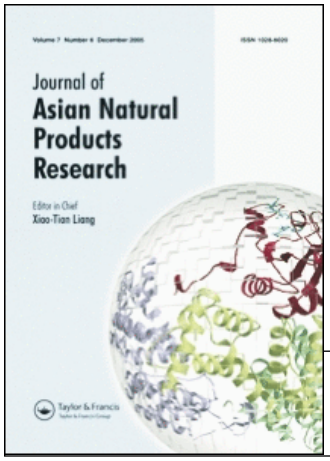

Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

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Qiong Gu [a]; Xue-Mei Zhang [a]; Jun Zhou [a]; Sheng-Xiang Qiu [a]; Ji-Jun Chen [a]
[a] State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, China

Online Publication Date: 01 June 2008

To cite this Article: Gu, Qiong, Zhang, Xue-Mei, Zhou, Jun, Qiu, Sheng-Xiang and Chen, Ji-Jun (2008) 'One new dihydrobenzofuran lignan from **Vitex trifolia**', Journal of Asian Natural Products Research, 10:6, 499 — 502

To link to this article: DOI: 10.1080/10286020801967359
URL: http://dx.doi.org/10.1080/10286020801967359

Journal of Asian Natural Products Research
Vol. 10, No. 6, June 2008, 499–502

One new dihydrobenzofuran lignan from *Vitex trifolia*

Qiong Gu[a,b], Xue-Mei Zhang[a], Jun Zhou[a,c], Sheng-Xiang Qiu[a] and Ji-Jun Chen[a,c]*

[a]*State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, China;* [b]*Graduate School of the Chinese Academy of Sciences, Beijing 100039, China;* [c]*The Joint-Laboratory of Anti-Viral Natural Medicines, Kunming Branch, the Chinese Academy of Sciences, Kunming 650204, China*

(*Received 7 November 2006; final version received 31 May 2007*)

A new benzofuran-type lignan, vitrifol A (**1**), was isolated from the fruits of *Vitex trifolia*, along with three known compounds **2**–**4**. Their structures were elucidated mainly on the basis of 1D, 2D NMR and MS spectral data. Compound **1** was first isolated as a dimer of dihydrobenzofuran-type lignan.

Keywords: *Vitex trifolia*; Verbenaceae; vitrifol A; dimer of dihydrobenzofuran

1. Introduction

Vitex trifolia L. (Verbenaceae) has long been used as a medicinal plant and is widely distributed in Asia, Australia, and East Africa. The ripened fruits of this plant, Viticis Fructus, have traditionally been used as a folk medicine in China for the treatment of headache, cold, migraine, eyepain, and rheumatism, and its leaves have also been used for the treatment of wounds.[1] In early reports, flavonoids,[2,3] sterols,[2] and diterpenes[4–7] were isolated from this plant. In this paper, we present the isolation and structural elucidation of one new compound, vitrifol A (**1**), along with three known compounds, dihydrodehydrodiconifenyl alcohol (**2**),[8] stigmast-4-en-6β-ol-3-one (**3**),[9] and eucommiol (**4**)[10] from *Vitex trifolia*. To our knowledge, all compounds were isolated from this plant for the first time.

2. Results and discussion

Compound **1** was obtained as pale yellow oil and has the molecular formula $C_{30}H_{34}O_9$ as deduced by its negative HR-ESI-MS at *m/z* 537.2139 $[M - H]^-$, requiring 14 degrees of unsaturation. The UV spectrum showed absorption maximum at 205 (4.84) nm, indicating the presence of an aromatic ring. The IR spectrum showed absorption bands at 3424, 1604, 1498 and 1465 cm^{-1}, revealing the presence of hydroxyl groups and aromatic rings. The ^1H NMR spectrum displayed signals at δ_H 6.86 (1H, d, $J = 1.8$ Hz), 6.81 (1H, m) and 6.79 (1H, d, $J = 8.1$ Hz) for an AMX spin system of a 1,3,4-trisubstituted aromatic A-ring and four singlets (4H) at δ_H 6.86, 6.84 and 6.62 for two tetrasubstituted aromatic ring with four benzylic methines. The remaining ^1H NMR signals indicated three methoxyl substituents, a *n*-propanol and two —O—CH—CH—CH_2O— spin systems. The ^{13}C NMR spectrum consisted of 30 resonances (Table 1), including 11 quaternary carbons, of which six were oxygenated aromatic; seven aromatic and four aliphatic methines, of which two were oxymethines; five methylenes, of which three were oxygenated; and three methoxyls (δ_C

*Corresponding author. Email: chenjj@mail.kib.ac.cn

ISSN 1028-6020 print/ISSN 1477-2213 online

DOI: 10.1080/10286020801967359
http://www.informaworld.com

Table 1. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectral data of compounds **1** and **2** ($CDCl_3$, δ in ppm).

	1		**2**	
No.	δ_H	δ_C	δ_H	δ_C
1		132.9 s		132.8 s
2	6.86 (1H, d, 1.8 Hz)	108.9 d	6.83 (1H, d, 1.5 Hz)	108.9 d
3		146.8 s		146.8 s
4		145.6 s		145.3 s
5	6.79 (1H, d, 8.1 Hz)	114.4 d	6.70 (1H, d, 8.1 Hz)	114.4 d
6	6.81 (1H, dd, 8.1, 1.8 Hz)	119.2 d	6.75 (1H, dd, 8.1, 1.5 Hz)	118.8 d
7	5.48 (1H, d, 7.5 Hz)	87.9 d	5.40 (1H, d, 6.9 Hz)	87.6 d
8	3.51–3.48 (1H, m)	53.6 d	3.43 (1H, m)	53.4 d
9	3.85 (2H, m)	63.4 t	3.52 (2H, m)	63.5 t
1′		134.7 s		135.1 s
2′	6.84 (1H, br s)	110.5 d	6.55 (1H, s)	112.0 d
3′		144.0 s		143.5 s
4′		148.2 s		145.8 s
5′		128.4 s		127.9 s
6′	6.86 (1H, br s)	114.4 d	6.57 (1H, s)	116.1 d
7′	5.49 (1H, d, 7.8 Hz)	88.3 d	2.51 (2H, t, 7.1 Hz)	31.5 t
8′	3.57–3.52 (1H, m)	53.8 d	1.73 (2H, m)	34.0 t
9′	3.76 (2H, m)	63.9 t	3.78 (2H, m)	61.3 t
1″		135.4 s		
2″	6.62 (1H, br s)	112.3 d		
3″		144.2 s		
4″		146.2 s		
5″		127.9 s		
6″	6.62 (1H, br s)	116.1 d		
7″	2.60 (2H, t, 7.5 Hz)	31.9 t		
8″	1.82 (2H, m)	34.4 t		
9″	3.61 (2H, t, 6.4 Hz)	61.8 t		
3-OMe	3.82 (s)	55.9 q	3.73 (s)	55.5 q
3′-OMe	3.80 (s)	55.9 q	3.67 (s)	55.5 q
3″-OMe	3.80 (s)	55.9 q		

56.0). By comparing the IR, UV and NMR spectral data for **1** with the literature,[11] it showed that compound **1** was a dimer of dihydrobenzofuran neolignan. In the HMBC spectrum (Figure 2), the observed cross-peaks of H-7′ (δ_H 5.49, IH, d, $J = 7.8$ Hz) with C-1′,C-2′,C-6′,C-8′,C-9′,C-4”,H-7 (δ_H 5.48, 1H,d,$J = 7.5$ Hz) with C-1,C-2,C-6,C-8,C-9 and C-4′,H-2′ (δ_H 6.84,1H, br s), H-6′ (δ_H 6.86,1H, br s) with C-7′, as well as the cross-peaks of H-2 (δ_H 6.86, IH, d, $J = 1.8$ Hz) and H-6(δ_H 6.81, IH, m) with C-7, suggested that one dihydrobenzofuran moiety was connected to 1,3,4-trisubstituted aromatic ring (A) and the

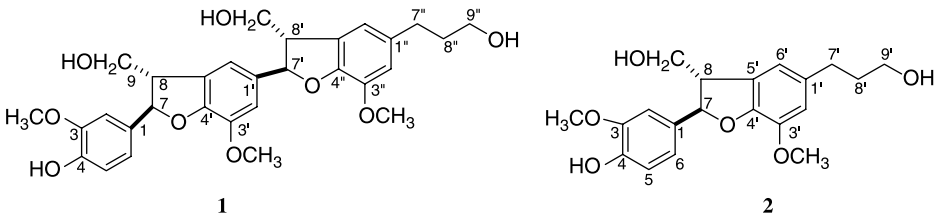

Figure 1. Structures of compounds **1**–**2**.

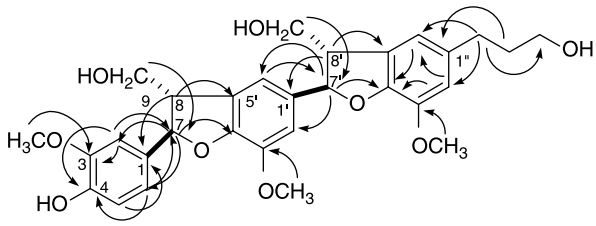

Figure 2. Key HMBC correlations of compound **1**.

other dihydrobenzofuran structure (B and C). In the ROESY spectrum (Figure 3), the correlations observed between H-7 and H-9,H-7′ and H-9′, and the correlations between H-2 and H-8, H-6′ and H-8′ indicated threo arrangements for phenyl and hydroxymethylene groups at the C-7 and C-8, C-7′ and C-8′. Comparison of the chemical shifts of C-7, C-8,C-9,C-7′,C-8′ and C-9′ of **1** with those of **2** established that compounds **1** and **2** had the same configuration, which were further confirmed by the ROSEY experiment (Figure 3) and the coupling constants of H-7 and H-7.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured with a Horiba SEPA-300 polarimeter. UV spectra were obtained using a Shimadzu UV-210A spectrophotometer. IR spectra were measured on a Bio-Rad FTS-135 spectrometer (Bio-Rad, Richmond, CA) with KBr pellets. MS spectra were performed on a VG Autospec-3000 spectrometer under 70 eV. 1D and 2D NMR spectra were recorded on Bruker AM-400 and DRX-500 spectrometer. Chemical shifts (δ) were expressed in ppm with reference to the solvent signals. Column chromatography was performed with silica gel (200–300 mesh, Qing-dao Marine Chemical Factory, Qingdao, China), silica gel H (60 μm, Qing-dao Marine Chemical Factory). Lichroprep RP-18 (43–63 μm, Merck, Darmstadt, Germany), MCI gel (75–150 μm, Mitsubishi Chemical Corporation, Japan) and Sephadex LH-20 (Pharmacia Fine Chemical Co. Ltd., Uppsala, Sweden) were also used for column chromatography. Fractions were monitored by TLC and spots were visualized by heating silica gel plates sprayed with 5% H_2SO_4 in EtOH.

3.2 Plant material

The fruits of *Vitex trifolia* were collected from Xishuangbanna, Yunnan Province, China, in May 2001, and identified by senior engineer Mr Jing-Yun Cui, Xishuangbanna Tropic Botanical Garden, the Chinese Academy of Sciences, where a voucher specimen (2001-2005) is deposited.

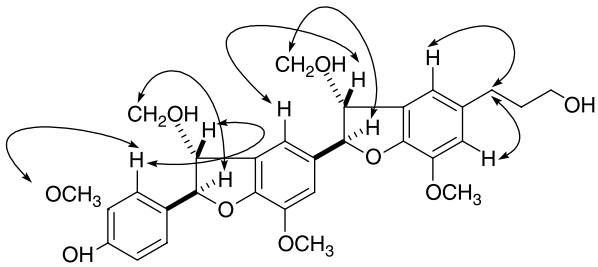

Figure 3. Key ROESY correlations of compound **1**.

3.3 Extraction and isolation

The n-BuOH extract (240 g) was subjected to silica gel column chromatography (10 × 150 cm, 200–300 mesh, 1500 g) eluting with $CHCl_3/MeOH/H_2O$ (from 9:1:0.1 to 7:3:0.3) to provide fractions A-J. Fraction A (10 g) was chromatographed on silica gel (4.5 × 60 cm, 200–300 mesh, 200 g) column with an elution of $CHCl_3/Me_2CO$ (from 9:1 to 7:3) to obtain fractions A_1-A_3. Fraction A_3 (3 g) was chromatographed on silica gel column (3 × 60 cm, 200–300 mesh, 90 g) eluting with $CHCl_3/Me_2CO$ (8:2), followed by recrystallizing in $CHCl_3$ to yield compound 3 (120 mg). Fraction B (15 g) was submitted to a silica gel column (4.5 × 60 cm, 200–300 mesh, 300 g) using gradient elution of $CHCl_3/Me_2CO$ (from 8:2 to 1:1) to obtain fractions B_1-B_5. Fraction B_3 (4 g) was performed on silica gel column (4.5 × 60 cm, silica gel H, 120 g) eluting with $CHCl_3$/EtOAc (7:3) to produce the mixture of compounds **1** and **2.** The mixture was repeatedly purified over silica gel (silica gel H) eluting with petroleum ether/EtOAc (2.5:7.5) to afford compounds **1** (10 mg) and **2** (20 mg). Fraction J (30 g) was decolorized on MCI gel CHP-20 (1.5 × 30 cm) with an elution of $MeOH/H_2O$ (90:10) to yield a pale yellow gum (15 g), which was subjected to silica gel, RP-18 (1.5 × 35 cm), and Sephadex LH-20 (1.5 × 60 cm) column subsequently to give compound **4** (727 mg).

3.3.1 *Vitrifol A (**1**)*

Pale yellow oil. $[\alpha]_D^{28} = +5.95$ ($c = 0.20$, MeOH); UV (MeOH) λ_{max} (log ε): 205 (4.84), 282 (3.80), 357 (2.51) nm; IR (KBr) ν_{max}: 3424, 2924, 2853, 1604, 1517, 1498, 1465, 1377, 1303, 1286, 1139, 1123, 1037, 982, 946, 852, 813, 744 cm^{-1}; ^1H and ^{13}C NMR spectral data (see Table 1); negative ESI-MS: *m/z* 537 $[M - H]^-$; negative HR-ESI-MS *m/z*: 537.2139 $[M - H]^-$ (calcd for $C_{30}H_{33}O_9$, 537.2124).

Acknowledgements

This study was financially supported by the Training Program of Qualified Person, the Department of Science and Technology, Yunnan Province (2005–2007) to Professor Ji-Jun Chen. The authors thank the members of the Analytical group of Kunming Institute of Botany for the measurements of UV, IR, MS and NMR spectral data. We are also grateful to Mr Jing-Yun Cui for collecting and identifying the plant materials.

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