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Lie-Chwen Lin^{a b c}, Tung-Hu Tsai^c & Shao-Chieh Su^a

^a National Research Institute of Chinese Medicine, Taipei 112, Taiwan

^b Graduate Institute of Integrated Medicine, China Medical University, Taichung 404, Taiwan

^c Institute of Traditional Medicine, National Yang-Ming University, Taipei 112, Taiwan

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A novel 8.O.6'-neolignan from *Taxillus theifer*

Lie-Chwen Lin^{abc*}, Tung-Hu Tsai^c and Shao-Chieh Su^a

^aNational Research Institute of Chinese Medicine, Taipei 112, Taiwan; ^bGraduate Institute of Integrated Medicine, China Medical University, Taichung 404, Taiwan; ^cInstitute of Traditional Medicine, National Yang-Ming University, Taipei 112, Taiwan

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A new 8.O.6'-neolignan, *threo*-(7R, 8R)-7-acetoxy-3',4'-dimethoxy-3,4-dimethoxy- Δ -⁸-8.O.6'-neolignan (**1**) along with two known lignans (**2**) and (**3**), was isolated from the leaves and stems of *Taxillus theifer*. Structural elucidation was carried out by 1-D and 2-D-NMR spectroscopic methods, and the absolute configurations of C-7 and C-8 in **1** were determined on the basis of circular dichroism. Compound **2** is *threo*-7-acetoxy-3'-methoxy-3,4-dimethoxy- Δ -⁷-8.O.4'-neolignan obtained from a natural source for the first time, previously derived from a synthesis study of 8,4'-oxyneolignans.

Keywords: *Taxillus theifer*; *Scurrula ritozanensis*; Loranthaceae; 8.O.6'-neolignan

1. Introduction

Taxillus theifer (Hayata) H.S. Kiu (*Scurrula ritozanensis*), a Loranthaceae plant endemic to Taiwan (Chiu, 1996), has been used as an antihypertensive agent in Formosan folk medicine. Flavonoids are the major components in the Loranthaceae plants and some of them have been identified with antihypertensive property (Fukunaga, Nishiya, Kajikawa, Takeya, & Itokawa, 1989). Our previous study showed that the ethanolic extract of *T. theifer* had a significant vasorelaxing effect on a vasoconstrictor-treated rat aortic ring preparation. Meanwhile, 11 flavonoids and a minor new catechin derivative were identified from *T. theifer* (Tsai, Liu, & Lin, 2010). In a continuing chemical examination of this plant, we isolated a new neolignan together with other two lignans from the leaves and stems of *T. theifer*. The known lignan (**3**) was identified as (7R, 8R, 3'R)-7-acetoxy-3',4'-dimethoxy-3,4-dimethoxy-6'-oxo- Δ -^{1',4',8'}-8.3'-lignan by comparison with spectroscopic data and authentic sample (Lin, C.C. Shen, Y.C. Shen, & Tsai, 2006; Prasad et al., 1994).

2. Results and discussion

Theiferin (**1**) was obtained as a colourless oil. The molecular formula of **1** was consistent with C₂₄H₃₀O₇ from the HR-EIMS spectrum *m/z* 430.1994 [M]⁺. The ¹H-NMR spectrum of **1** exhibited an allyl group [methylene protons at δ 3.21 (m)

*Corresponding author. Email: lclin@nricm.edu.tw

and olefinic protons at δ 5.87(m)/4.94/4.97], and an acetoxy methyl at δ 2.13 (s). In addition, a doublet at δ 1.25 (3H, J = 6.5 Hz), a multiplet at δ 4.62 (1H) and a doublet at δ 5.83 (1H, J = 4.5 Hz) represented the typical AMX₃-type signal of a CH₃–CH–(O)–CH–(O)– unit. A set of ABC-type signals at δ 6.91 (d, J = 8.0 Hz)/6.96 (dd, J = 8.0, 2.0 Hz)/6.99 (d, J = 2.0 Hz) and two aromatic methoxy methyl singlets at δ 3.80 (6H, s) suggested that a veratryl group was present. Other two aromatic singlet at δ 6.55/6.68 and two aromatic methoxy methyl singlet at δ 3.74/3.76 were assigned to the dimethoxyl-1,3,4,6-tetrasubstituted ring system. As expected, the ¹³C-NMR chemical shift at δ 123.1 (C-1', s), 115.8 (C-2', d), 145.1 (C-3', s), 149.6 (C-4', s), 102.6 (C-5', d) and 150.5 (C-6', s) agreed with the 1,3,4,6-tetrasubstituted ring system. The presence of the veratryl ring system, allyl group and CH₃–CH–(O)–CH–(O)– unit was further confirmed by the ¹H–¹H-COSY spectrum. The connection of the above units was established in HMBC (Figure 1) and INAPT (Figure S1 – online only) experiments. The HMBC spectrum showing the correlation of H-2, H-5, H-7 and H-8 with C-1; H-5' and H-7' with C-1'; H-2', H-5', H-7' and H-8 with C-6'; and H-7 and H- β with acetyl carbonyl C- α suggested the 8.O.6'-neolignan linking of **1**. In the INAPT experiments, signals of H-7' (δ 3.21) and H-8 (δ 4.62) were excited individually; the interaction carbon signals of C-1', C-2', C-6' and C-8' for H-7'; and C-1 and C-6' for H-8 were observed, clearly pointing out the linkage of 8.O.6'-neolignan. The NOESY spectrum showing the correlations of H-2 with H-7 and 3-OCH₃; H-5 with H-6 and 4-OCH₃; H-2' with H-7' and 3'-OCH₃; H-5' with H-8 and 4'-OCH₃ indicated the position of 3-, 4-, 3'- and 4'-OCH₃. Therefore, compound **1** was identified as 7-acetoxy-3', 4'-dimethoxy-3, 4-dimethoxy- Δ -8'- 8.O.6'-neolignan. The NMR characteristics of coupling constant ($J_{7,8}$ = 4.5 Hz) and the C-7 signal at δ_{C} 78.6 suggested that compound **1** had a *threo*-configuration (Braga, Zacchino, Badano, Sierra, & Ruveda, 1984). The NOESY correlations of H-7 with H-8 and H-9 also indicated the *threo* relative configuration (Machida, Sakamoto, & Kikuchi, 2009). The absolute stereochemistry of **1** was deduced as (7R, 8R) on the basis of the negative Circular dichroism (CD) Cotton effects (Figure S2 – online only) (Konya, Kurtan, Kiss-Szikszai, Juhász, & Antus, 2004). Therefore, **1** was deduced as *threo*-(7R, 8R)-7-acetoxy-3',4'-dimethoxy-3,4-dimethoxy- Δ -8'- 8.O.6'-neolignan.

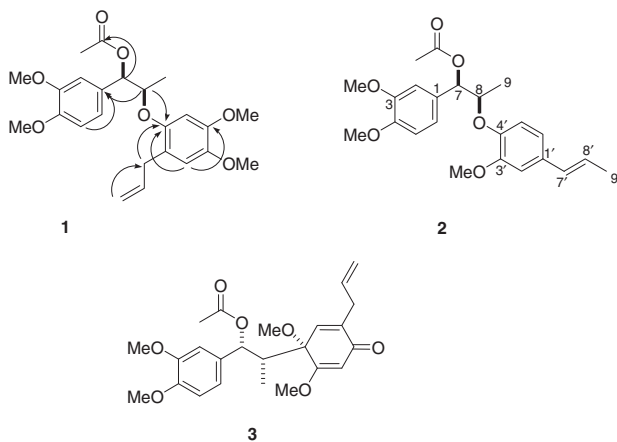


Figure 1. Chemical structures of neolignans **1**–**3** and key HMBC correlations of compound **1**.

Compound **2** was obtained as an oil. The molecular formula of **2** was consistent with $C_{23}H_{28}O_6$ from the HR-EIMS spectrum m/z 400.1893 $[M]^+$. The 1H -NMR spectrum of **2** showed a propenyl group [methyl protons at δ 1.85 (d, $J = 6.5$ Hz), and olefinic protons at δ 6.34 (d, $J = 15.0$ Hz)/6.15 (dq, $J = 15.0, 6.5$ Hz)], a $CH_3-CH(O)-CH(O)-$ unit [δ 1.11 (3H, d, $J = 6.5$ Hz)/ δ 4.66 (1H, dq, $J = 7.0, 6.5$ Hz)/ δ 5.81 (1H, d, $J = 7.0$ Hz)], an acetoxy methyl at δ 1.96 (s), three aromatic methoxy methyl singlet at δ 3.82/3.83 and two sets of ABC-type signals (δ 6.94/6.94/6.99 and δ 6.92/6.85/6.97). The presence of 1,3,4-trisubstituted ring systems, propenyl group and $CH_3-CH(O)-CH(O)-$ unit was confirmed by the $^1H-^1H$ -COSY spectrum. The HMBC spectrum showing the correlation of H-2, H-5, H-7 and H-8 with C-1; H-5' and H-7' with C-1'; H-2', H-5', H-7' and H-8 with C-6'; and H-7 and H- β with acetyl carbonyl C- α confirmed the proposed structure of **2**. HMBC correlations between H-2/C-4, C-6, C-7; H-5'/C-1', C-3'; H-6'/C-2', C-4', C-7'; and H-8'/C-1', and H-7, H- β /C- α indicated the 8.O.4'-neolignan linking of **2**. The NOESY correlations between 3-OCH₃/H-2; 4-OCH₃/H-5; and 3'-OCH₃/H-2' indicated the position of 3-, 4- and 3'-OCH₃. The signal of C-7 at δ_C 80.0 suggested that compound **2** had a *threo*-configuration (Braga et al., 1984). On the basis of these spectral data, **2** was deduced as *threo*-7-acetoxy-3'-methoxy-3,4-dimethoxy- Δ -⁷-8.O.4'-neolignan. Compound **2** is an acetate derivative of virolin. This is the first time **2** has been isolated from a natural source, although **2** had been derived from a synthesis study of 8-4'-oxyneolignans (Curti et al., 2006). Virolin was primarily identified from the anti-schistosomiasis plant *Virola surinamensis* (Myristicaceae) (Barata, Baker, Gottlieb, & Ruveda, 1978).

3. Experimental

3.1. General experiment procedures

UV spectra were measured on a Hitachi U-3200 spectrophotometer in MeOH. Optical rotations were recorded on a Jasco-DIP-370 polarimeter. CD spectra were recorded on Jasco J-715 spectrometer. 1H -, ^{13}C - and 2-D-NMR spectra were measured with a Varian Inova-500 spectrometer with deuterated solvents as internal standard. ESI-MS and HR-EIMS were recorded on Finnigan LCQ and Finnigan MAT 95S MS spectrometers, respectively. Column chromatography was performed on Sephadex LH-20 (Pharmacia). Silica gel 60F₂₅₄ (Merck, Darmstadt, Germany) was used for TLC (0.25 mm) and preparative TLC (1 mm). The preparative HPLC system consisted of a chromatographic pump (LC-8A, Shimadzu, Kyoto, Japan) and a UV-Visible detector (SPD-10A vp, Shimadzu, Kyoto, Japan). A Cosmosil 5C₁₈-AR-II column (10 \times 250 mm; particle size 5 μ m; Nacalai tesque, Kyoto, Japan) was used for separation.

3.2. Plant material

The leaves and stems of *T. theifer* were collected on March 2007, in Nantou, Taiwan, and verified by Dr Cheng-Jen Chou, research fellow of National Research Institute of Chinese Medicine, Taipei, Taiwan. A voucher specimen (LCL-068) has been deposited in the National Research Institute of Chinese Medicine, Taipei, Taiwan.

3.3. Extraction and isolation

The leaves and stems of *T. theifer* (5.0 kg) were collected. The leaves and stems of *T. theifer* were extracted with ethanol (40 L \times 3) under reflux. The ethanolic extract was evaporated to dryness and partitioned successively between H₂O and *n*-hexane, followed by *n*-BuOH (each 1 L \times 3). The *n*-BuOH fraction (103 g) was subjected to column chromatography on Sephadex LH-20 (10 \times 120 cm), with a gradient of MeOH in H₂O from 50% to 100%, and 12 fractions (Fr. 1~12) were collected. Fraction 11 (0.34 g) was further purified by Sephadex LH-20 (GE Healthcare Biosciences AB, Sweden) eluting with 5% CHCl₃/MeOH to get sub fractions 11A-11C. Fractions 11B was chromatographed on a preparative TLC (40% EtOAc/*n*-hexane), and on a preparative HPLC (column: Cosmosil 5C18-AR-II, 10 \times 250 mm, 5 μ m, solvent: 60% ACN/H₂O, flow rate: 6 mL min⁻¹) to give **1** (23.1 mg), **2** (9.9 mg) and **3** (11.1 mg).

3.3.1. *Theiferin*; *threo*-(7*R*, 8*R*)-7-*acetox*y-3',4'-*dimethoxy*-3,4-*dimethoxy*- Δ -8'-8.0.6'-*neolignan* (**1**)

Viscous oil; $[\alpha]_D^{25} + 28.4^\circ$ (*c* 1.48, MeOH); UV (MeOH) λ_{\max} (log ϵ) 284 (3.83), 232 (4.28) nm; ¹H-NMR (500 MHz, CD₃OD) δ 6.99 (1H, d, *J* = 2.0 Hz, H-2), 6.91 (1H, d, *J* = 8.0 Hz, H-5), 6.96 (1H, dd, *J* = 8.0, 2.0 Hz, H-6), 5.83 (1H, d, *J* = 4.5 Hz, H-7), 4.62 (1H, m, H-8), 1.25 (3H, d, *J* = 6.5 Hz, H-9), 6.68 (1H, s, H-2'), 6.55 (1H, s, H-5'), 3.21 (2H, m, H-7'), 5.87 (1H, m, H-8'), 4.94/4.97 (2H, m, H-9'), 2.13 (3H, s, C=OCH₃), 3.74 (3H, s, 3'-OCH₃), 3.76 (3H, s, 4'-OCH₃) and 3.80 (6H, s, 3-OCH₃, 4-OCH₃); ¹³C NMR (125 MHz, CD₃OD) δ 131.5 (C-1), 112.4 (C-2), 150.3 (*C-3), 150.4 (*C-4), 112.7 (C-5), 121.3 (C-6), 78.6 (C-7), 78.5 (C-8), 15.9 (C-9), 123.1 (C-1'), 115.8 (C-2'), 145.1 (C-3'), 149.6 (C-4'), 102.6 (C-5'), 150.5 (C-6'), 34.8 (C-7'), 138.7 (C-8'), 115.4 (C-9'), 171.7 (C=OCH₃), 21.1 (C=OCH₃), 56.5 (-OCH₃ \times 2), 56.9 (-OCH₃), 57.3 (-OCH₃); ESIMS *m/z* 453 [M + Na]⁺; HREIMS *m/z* 430.1994 (calcd for C₂₄H₃₀O₇, 430.1992); CD [nm ($\Delta\epsilon$)] (5.16 mg/100 mL MeOH): 277 (-0.56), 264 (-0.21), 243 (-4.02) and 230 (+3.20).

3.3.2. *Threo*-7-*acetox*y-3'-*methoxy*-3,4-*dimethoxy*- Δ -7'-8.0.4'-*neolignan* (**2**)

Viscous oil; $[\alpha]_D^{25} - 35.7^\circ$ (*c* 0.14, MeOH); λ_{\max} (log ϵ) 286 sh. (3.59), 2.69 (3.90), 259 (3.91) nm; ¹H-NMR (500 MHz, CD₃OD) δ 6.99 (1H, br. s, H-2), 6.94 (2H, m, H-5, -6), 5.81 (1H, d, *J* = 7.0 Hz, H-7), 4.66 (1H, dq, *J* = 7.0, 6.5 Hz, H-8), 1.11 (3H, d, *J* = 6.5 Hz, H-9), 6.97 (1H, d, *J* = 2.0 Hz, H-2'), 6.92 (1H, d, *J* = 8.0 Hz, H-5'), 6.85 (1H, dd, *J* = 8.0, 2.0 Hz, H-6'), 6.34 (1H, d, *J* = 15.0 Hz, H-7'), 6.15 (1H, dq, *J* = 15.0, 6.5 Hz, H-8'), 1.85 (3H, d, *J* = 6.5 Hz, H-9'), 1.96 (3H, s, C=OCH₃) and 3.82/3.83 (9H, -OCH₃); ¹³C-NMR (125 MHz, CD₃OD) δ 131.5 (C-1), 112.5 (C-2), 150.4 (*C-3), 150.7 (*C-4), 112.7 (C-5), 121.4 (C-6), 80.0 (C-7), 79.0 (C-8), 17.0 (C-9), 134.0 (C-1'), 111.1 (C-2'), 151.8 (C-3'), 148.2 (C-4'), 118.2 (C-5'), 119.9 (C-6'), 131.9 (C-7'), 124.9 (C-8'), 18.5 (C-9'), 172.0 (C=OCH₃), 21.0 (C=OCH₃) and 56.5 (-OCH₃); ESIMS *m/z* 423 [M + Na]⁺; HREIMS *m/z* 400.1893 [M]⁺ (calcd for C₂₃H₂₈O₆, 400.1886).

Supplementary material

Figures S1 and S2 relating to this paper are available online.

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