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## Glycosides from the Root of *Iodes cirrhosa*

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Seven new neolignan glycosides (**1–7**), two arylglycerol glycosides (**8, 9**), and 18 known glycosides have been isolated from an ethanolic extract of the root of *Iodes cirrhosa*. Their structures including absolute configurations were determined by spectroscopic and chemical methods. Based on analysis of the NMR data of *threo* and *erythro* 8-4'-oxyneolignans and arylglycerols in different solvents, the validity of  $J_{7,8}$  and  $\Delta\delta_{C8-C7}$  values to distinguish *threo* and *erythro* derivatives was discussed. In the *in vitro* assays, compound **4** and liriiodendrin (**17**) both showed activity against glutamate-induced PC12 cell damage at  $10^{-5}$  M.

*Iodes* (Icacinaeae) species are woody climber plants, widely distributed in southeastern Asia, especially in southern China. *Iodes cirrhosa* Turcz. is one of several *Iodes* species used in traditional Chinese medicine. Extracts of the root and stem are reported to improve general blood circulation and are used for treatment of inflammatory and rheumatic diseases.<sup>1</sup> There have been no previous reports concerning the secondary metabolites from this genus. As part of a program to assess the chemical and biological diversity of traditional Chinese medicines,<sup>2,3</sup> an ethanolic extract of the root of *I. cirrhosa* has been investigated. We describe herein isolation and structural elucidation of seven new neolignan glycosides (**1–7**), two new arylglycerol glycosides (**8, 9**), and 18 known glycosides. Compounds **1–3** are unusual 8-4'-oxyneolignan glycosides with a glycosyloxy group at C-3', while **7** is an unusual dihydro[*b*]benzofuran neolignan glycoside with an aromatic ring at C-8'. Since the assignment of some of the *erythro* and *threo* 8-4'-oxyneolignan and arylglycerol derivatives is ambiguous in the literature,<sup>4–9</sup> the validity of  $J_{7,8}$  and  $\Delta\delta_{C8-C7}$  values to distinguish *threo* and *erythro* 8-4'-oxyneolignan and arylglycerol derivatives is discussed on the basis of NMR data of *threo* and *erythro* 8-4'-oxyneolignans and arylglycerols in different solvents. Some *in vitro* bioassays are also reported.

### Results and Discussion

Compound **1** was obtained as an amorphous solid, and the presence of OH ( $3358\text{ cm}^{-1}$ ) and aromatic ( $1602$  and  $1509\text{ cm}^{-1}$ ) groups were indicated by its IR spectrum. The positive mode ESIMS of **1** gave a quasi-molecular ion peak at  $m/z$  547  $[M + Na]^+$ , and the molecular formula  $C_{25}H_{32}O_{12}$  was indicated by HRFABMS at  $m/z$  547.1801. The  $^1\text{H}$  NMR of **1** in DMSO- $d_6$  showed signals attributed to two 1,3,4-trisubstituted aromatic rings at  $\delta$  6.97 (H-2), 6.68 (H-5), and 6.80 (H-6), and 7.19 (H-2'), 6.89 (H-5'), and 6.93 (H-6'), together with signals attributed to an aromatic methoxy at  $\delta$  3.72 and an exchangeable phenolic OH proton at  $\delta$  8.80 (OH-4). A *trans*-arylpropenoxy unit was indicated by signals at  $\delta$  6.41 (H-7'), 6.21 (H-8'), and 4.06 (H-9'). Meanwhile, an arylglyceryloxy unit was indicated by signals of a vicinal coupling system attributed to two oxymethines at  $\delta$  4.69 (H-7) and 4.27 (H-8) and an oxymethylene at  $\delta$  3.63 (H-9a) and 3.51 (H-9b). A doublet assignable to an anomeric proton at  $\delta$  4.79, partially overlapped signals attributed to oxymethylene and oxymethine protons between  $\delta$  3.13 and 3.70, and exchangeable OH protons between  $\delta$  4.50 and 5.35 suggested that there was a  $\beta$ -glycosyl moiety in **1**. Enzymatic hydrolysis of **1** produced **1a** and a sugar. The sugar

gave a positive optical rotation,  $[\alpha] +47.2$ , indicating that it was D-glucose.<sup>10</sup> The  $^{13}\text{C}$  NMR and DEPT spectra of **1** showed carbon signals corresponding to the above units (Table 2). The presence of four oxygen-bearing aromatic carbons ( $\delta > 145$  ppm) in the  $^{13}\text{C}$  NMR spectrum, in combination with the chemical shifts and coupling patterns of the protons of the two aromatic rings in the  $^1\text{H}$  NMR spectrum and the molecular composition, suggested that **1** was a 8-4'-oxyneolignan  $\beta$ -D-glucopyranoside with one phenolic OH and one aromatic methoxy groups. However, the spectroscopic data of **1** were different from those of related known compounds.<sup>11–13</sup>

Extensive analysis of HMQC and  $^1\text{H}$ - $^1\text{H}$  COSY spectra of **1** provided unambiguous assignments of proton and carbon signals in the NMR spectra. In the HMBC spectrum of **1**, long-range correlations from H-7 to C-1, C-2, C-6, C-8, and C-9 and from H-7' to C-1', C-2', C-6', C-8', and C-9' (Figure S1, Supporting Information), in combination with chemical shifts and coupling patterns, confirmed the presence of 3,4-disubstituted phenylglyceryloxy and 3',4'-disubstituted *trans*-phenylpropenoxy units. HMBC correlations of C-3 with H-2, H-5, and the methoxy protons and of C-4 with H-2 and H-6 proved that the methoxy was located at C-3. Correlations of C-3' with H-2', H-5', and the anomeric proton and of C-4' with H-2' and H-6', and the chemical shift of C-3', indicated that the glucose was attached at C-3'. This conclusion was supported by NOE enhancements of H-7', H-8', and H-1'' by irradiation of H-2' in the NOE difference experiment (Figure S1, Supporting Information). Although a correlation from H-8 to C-4' was not observed in the HMBC spectrum of **1**, NOE enhancements of H-2, H-6, and H-5' by irradiation of H-8 indicated a connection between C-8 and C-4' in **1**.

The stereochemistry of **1** was elucidated by a comprehensive analysis of the NMR and CD data of **1**, **1a**, and the acetamide **1b**. The  $^1\text{H}$  NMR spectra of **1a** and **1b** (Table S1, Supporting Information) showed  $J_{7,8}$  values of 4.2 and 9.0 Hz, respectively. This suggested that **1** possessed an *erythro* relative configuration.<sup>11,12,14–18</sup> The CD spectra of **1** and **1a** showed negative Cotton effects at 233 and 236 nm (Figures S2 and S3, Supporting Information), respectively, indicating 8*R* configuration for these compounds.<sup>18,19</sup> Thus, **1** was determined to be (–)-(7*S*,8*R*,7'*E*)-4,7,9,3',9'-pentahydroxy-3-methoxy-8-4'-oxyneolign-7'-ene-3'-O- $\beta$ -D-glucopyranoside.

Compound **2** was obtained as an amorphous powder, and the molecular formula  $C_{25}H_{34}O_{12}$  was indicated by HRESIMS at  $m/z$  549.1963  $[M + Na]^+$ . The UV, IR, and NMR spectroscopic data of **2** indicated that it was a diastereomer of (7*R*,8*R*)-4,7,9,9'-tetrahydroxy-3-methoxy-8-O-4'-neolignan-3'-O- $\beta$ -D-glucopyranoside,<sup>15</sup> which was confirmed by the HMBC experiment of **2**. Hydrolysis of **2** with  $\beta$ -glucosidase liberated **2a** and D-glucose. The

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Table 1. <sup>1</sup>H NMR Data for Compounds 1–7<sup>a</sup>

no.	1	2	3	4	5	6	7 <sup>b</sup>
1a							
1b							
2	6.97 brs	6.97 brs	6.88 brs	6.95 d (1.5)	6.96 d (1.5)	4.07 dd (10.5, 5.0) 3.80 dd (10.5, 5.0) 4.54 quint (5.0) 3.77 dd (12.0, 5.0) 3.74 dd (12.0, 5.0)	6.92 brs
3a							
3b							
5	6.68 d (8.0)	6.68 d (8.0)	6.64 d (8.0)	6.69 d (8.0)	6.67 d (8.0)	7.24 d (2.0)	7.04 d (8.0)
6	6.80 brd (8.0)	6.78 brd (8.0)	6.67 brd (8.0)	6.75 dd (8.0, 1.5)	6.75 dd (8.0, 1.5)	7.13 d (8.0)	6.80 brd (8.0)
7	4.69 d (5.5)	4.69 d (5.5)	4.72 d (4.5)	4.69 d (4.5)	4.68 d (4.5)	7.20 dd (8.0, 2.0)	5.46 d (5.5)
8	4.27 ddd (6.0, 5.5, 3.0)	4.18 ddd (5.5, 5.0, 3.5)	4.24 ddd (6.0, 4.5, 3.0)	3.93 ddd (6.5, 4.5, 3.5)	4.16 ddd (5.5, 4.5, 4.0)	7.55 d (16.0)	3.35 m
9a	3.63 dd (12.0, 6.0)	3.62 dd (11.0, 5.0)	3.70 dd (11.5, 6.0)	3.58 dd (11.5, 6.5)	3.55 dd (11.0, 4.0)	6.63 dd (16.0, 7.5)	3.60 m
9b	3.51 dd (12.0, 3.0)	3.48 dd (11.0, 3.5)	3.38 dd (11.5, 3.0)	3.48 d (11.5, 3.5)	3.22 dd (11.0, 5.5)	9.54 d (7.5)	3.49 m
2'	7.19 d (1.0)	6.94 d (2.0)	6.90 d (1.5)	6.60 d (1.5)	6.81 d (1.5)		6.55 brs
5'	6.89 d (8.0)	6.82 d (8.0)		6.65 d (8.0)	6.90 d (8.5)		
6'	6.93 dd (8.0, 1.0)	6.70 dd (8.0, 2.0)	6.77 d (1.5)	6.39 dd (8.0, 1.5)	6.66 dd (8.5, 1.5)		6.60 brs
7'	6.41 d (16.0)	2.47 t (7.0)	6.43 d (16.0)	2.46 t (7.0)	2.56 t (7.5)		4.83 brs
8'	6.21 dt (16.0, 5.0)	1.66 quint (7.0)	6.31 dt (16.0, 5.0)	1.73 quint (7.0)	1.78 m		2.70 m
9'a	4.06 d (5.0)	3.37 t (7.0)	4.08 d (5.0)	3.74 dt (10.0, 7.0)	3.79 dt (10.0, 6.0)		3.69 m
9'b				3.38 dt (10.0, 7.0)	3.39 dt (10.0, 7.0)		3.47 m
1''	4.79 d (7.0)	4.75 d (7.5)	4.80 d (7.0)	4.09 d (8.0)	4.09 d (8.0)	4.29 d (7.5)	4.87 d (7.5)
2''	3.27 m	3.26 m	3.28 m	2.94 dd (8.5, 8.0)	2.95 dd (8.0, 8.0)	3.14 dd (8.5, 7.5)	3.23 m
3''	3.29 m	3.30 m	3.26 m	3.12 dd (8.5, 8.5)	3.14 dd (8.0, 8.0)	3.23 dd (8.5, 8.5)	3.24 m
4''	3.15 dd (9.0, 8.5)	3.14 m	3.12 m	3.03 dd (8.5, 8.5)	3.02 dd (8.0, 8.5)	3.23 dd (9.0, 8.5)	3.14 m
5''	3.26 m	3.25 m	3.28 m	3.04 m	3.07 m	3.29 m	3.24 m
6'a	3.68 brd (11.5)	3.66 brd (12.0)	3.69 brd (11.5)	3.64 brd (12.0)	3.63 dd (12.0, 2.0)	3.81 dd (11.5, 2.0)	3.66 dd (12.0, 2.0)
6'b	3.46 dd (11.5, 5.5)	3.46 dd (12.0, 5.5)	3.48 dd (11.5, 5.5)	3.43 dd (12.0, 5.0)	3.41 dd (12.0, 6.0)	3.60 dd (11.5, 5.0)	3.46 dd (12.0, 5.0)
3-OMe	3.72 s	3.72 s	3.72 s	3.71 s	3.68 s		3.73 s
3'/5'-OMe			3.74 s		3.70 s	3.84 s	3.63 s

<sup>a</sup> <sup>1</sup>H NMR data (δ) were measured in DMSO-d<sub>6</sub> for 1–5 and 7 and MeOH-d<sub>4</sub> for 6 at 500 MHz. Proton coupling constants (*J*) in Hz are given in parentheses. The assignments were based on DEPT, <sup>1</sup>H–<sup>1</sup>H COSY, HMQC, and HMBC experiments. <sup>b</sup> Data of the 3''-methoxy-4'''-hydroxyphenyl unit at C-7' of 7, δ 6.56 (1H, brs, H-2''), 6.58 (1H, d, *J* = 8.0 Hz, H-5''), 6.48 (1H, brd, *J* = 8.0 Hz, H-6''), 3.61 (3H, s, OMe-3'').

**Table 2.** <sup>13</sup>C NMR Data for Compounds **1–7**<sup>a</sup>

no.	1	2	3	4	5	6	7 <sup>b</sup>
1	132.9	133.0	132.7	132.7	133.0	69.1	135.6
2	111.2	111.2	111.0	111.4	111.0	80.5	110.2
3	147.1	147.0	147.1	147.1	147.0	62.0	148.9
4	145.5	145.4	145.5	145.6	145.4		146.1
5	114.8	114.8	114.8	114.8	114.6		115.3
6	119.6	119.6	119.3	119.4	119.0		117.8
7	71.4	71.3	71.6	71.8	71.0		86.5
8	85.6	85.9	86.4	87.0	84.8		53.5
9	59.9	59.8	59.6	60.2	60.1		63.4
1'	131.0	136.0	132.4	136.5	134.8	129.6	138.4
2'	115.3	117.9	108.0	116.5	112.9	112.7	110.8
3'	148.4	148.2	151.2	149.7	149.5	151.9	142.8
4'	147.9	146.4	135.4	144.9	146.4	151.9	145.9
5'	118.5	118.8	153.0	119.3	116.0	117.2	127.6
6'	120.8	122.3	104.8	117.8	120.2	124.5	114.9
7'	128.2	31.1	128.4	31.0	31.1	155.4	72.5
8'	129.1	34.1	130.3	31.1	31.2	127.9	55.2
9'	61.5	60.1	61.5	67.8	67.9	196.1	62.6
1''	101.8	101.8	101.8	102.9	103.0	104.7	100.1
2''	73.6	73.6	73.6	73.4	73.5	75.0	73.2
3''	76.4	76.4	76.3	76.7	76.7	78.0	76.8
4''	69.8	69.7	69.9	70.0	70.0	71.6	69.6
5''	77.1	77.0	77.3	76.8	76.8	78.0	77.0
6''	60.8	60.7	60.8	61.0	61.1	62.8	60.6
3-OMe	55.7	55.7	55.6	55.6	55.4	56.6	55.7
3'/5'-OMe			56.0		55.6		55.5
Δδ <sub>C8–C7</sub>	14.2	14.6	14.8	15.2	13.8		

<sup>a</sup> <sup>13</sup>C NMR data (δ) were measured in DMSO-*d*<sub>6</sub> for **1–5** and **7** and MeOH-*d*<sub>4</sub> for **6** at 125 MHz. The assignments were based on DEPT, <sup>1</sup>H–<sup>1</sup>H COSY, HMQC, and HMBC experiments. <sup>b</sup> Data of the 3'''-methoxy-4'''-hydroxyphenyl unit at C-7' of **7**, δ 131.2 (C-1'''), 113.9 (C-2'''), 146.5 (C-3'''), 144.7 (C-4'''), 114.5 (C-5'''), 121.8 (C-6'''), 55.4 (OMe-3''').

<sup>1</sup>H NMR spectra of **2a** and its acetonide **2b** in CDCl<sub>3</sub> showed *J*<sub>7,8</sub> values of 3.6 and 9.0 Hz (Table S1, Supporting Information), respectively, suggesting that **2** possessed an *erythro* relative configuration.<sup>11,17</sup> The CD spectra of **2** and **2a** displayed positive Cotton effects at 237 and 238 nm (Figures S2 and S3, Supporting Information), respectively, indicating that **2** and **2a** possessed an 8*S* configuration.<sup>18,19</sup> Therefore, **2** was determined to be (–)-(7*R*,8*S*)-4,7,9,3',9'-pentahydroxy-3-methoxy-8-4'-oxyneolignan-3'-*O*-β-D-glucopyranoside.

Compound **3** was obtained as an amorphous powder, and its HRESIMS at *m/z* 577.1851 [M + Na]<sup>+</sup> indicated the molecular formula C<sub>26</sub>H<sub>34</sub>O<sub>13</sub>. The UV, IR, and NMR spectroscopic features of **3** were similar to those of **1**, except that the NMR signals of the 3',4'-disubstituted *trans*-arylpropenoxy unit in **1** were replaced by those attributed to a 3',4',5'-trisubstituted *trans*-arylpropenoxy unit and a methoxy in **3** (Tables 1 and 2). These data indicated that **3** was an analogue of **1** with an additional methoxy at C-5'. This was confirmed by the HMBC spectrum of **3**, which showed correlations of C-3' with H-2' and H-1'', C-4' with H-2' and H-6', and C-5' with H-6' and the additional methoxy protons. An *erythro* configuration of **3** was confirmed by the *J*<sub>7,8</sub> (4.2 Hz) of **3a** in CDCl<sub>3</sub>. In the CD spectra of **3** and **3a**, respective negative Cotton effects at 235 and 236 nm (Figures S2 and S3, Supporting Information) indicated that they had 8*R* configuration. Therefore, **3** was determined to be (–)-(7*S*,8*R*,7'*E*)-4,7,9,3',9'-pentahydroxy-3,5'-dimethoxy-8-4'-oxyneolign-7'-ene-3'-*O*-β-D-glucopyranoside.

Compound **4** was assigned the molecular formula C<sub>25</sub>H<sub>34</sub>O<sub>12</sub>, as indicated by HRESIMS. The NMR data suggested that **4** was an isomer of **2**. The anomeric proton of **4** was shielded Δδ 0.66 ppm by comparison with that of **2**, while two multiplets at δ 3.74 (H-9'a) and 3.38 (H-9'b) in **4** replaced the triplet of H<sub>2</sub>-9' in **2**. This indicated that the glucopyranosyloxy moiety was located at C-9' in **4**, which was confirmed by the HMBC experiment of **4** showing correlations from both H-9'a and H-9'b to C-1'' and from H-1'' to

C-9'. The *J*<sub>7,8</sub> (3.6 Hz) of **4a** in CDCl<sub>3</sub> (Table S1) suggested that **4** had an *erythro*-configuration. In the CD spectra of **4** and **4a**, a positive Cotton effect at 238 nm (Figures S2 and S3) suggested that they both had an 8*S* configuration. Consequently, **4** was determined to be (–)-(7*R*,8*S*)-4,7,9,3',9'-pentahydroxy-3-methoxy-8-4'-oxyneolignan-9'-*O*-β-D-glucopyranoside.

The NMR data of **5** (Tables 1 and 2) were in good agreement with those of (–)-(7*R*,8*R*)-4,7,9,9'-tetrahydroxy-3,3'-dimethoxy-8-*O*-4'-neolignan-9'-*O*-β-D-glucopyranoside.<sup>15</sup> However, the optical rotation and CD data of **5** and its aglycone **5a** (Figures S2 and S3) were opposite of that reported. Therefore, the structure of **5** was assigned as (+)-(7*S*,8*S*)-4,7,9,9'-tetrahydroxy-3,3'-dimethoxy-8-4'-oxyneolignan-9'-*O*-β-D-glucopyranoside. This was supported by the <sup>1</sup>H NMR data of **5a** and its acetonide **5b** in CDCl<sub>3</sub>, which displayed *J*<sub>7,8</sub> values of 8.4 and ~0.0 Hz (Table S2), respectively.

Compound **6** was obtained as an amorphous powder, and its IR spectrum showed absorption bands for OH (3379 cm<sup>-1</sup>), conjugated CO (1662 cm<sup>-1</sup>), and aromatic (1595 and 1511 cm<sup>-1</sup>) groups. The molecular formula C<sub>19</sub>H<sub>26</sub>O<sub>10</sub> of **6** was indicated by HRFABMS. The NMR spectra of **6** in MeOH-*d*<sub>4</sub> displayed resonances due to glyceryl, 3',4'-disubstituted *trans*-phenylpropenal, and β-glucopyranosyl moieties and to a methoxy signal (Tables 1 and 2). Enzymatic hydrolysis of **6** yielded D-glucose and **6a**. The <sup>1</sup>H NMR and ESIMS spectroscopic data of **6a** were consistent with those of 2-{2-methoxy-4-[(*E*)-formylvinyl]phenoxy}propan-1,3-diol.<sup>20</sup> The HMBC experiment of **6** revealed that it was 1-*O*-β-D-glucopyranosyl-2-{2-methoxy-4-[(*E*)-formylvinyl]phenoxy}propan-3-ol. The negative optical rotation of **6** suggested that it had a 2*R* configuration.<sup>21</sup> Therefore, **6** was determined to be as (–)-(2*R*)-1-*O*-β-D-glucopyranosyl-2-{2-methoxy-4-[(*E*)-formylvinyl]phenoxy}propane-3-ol.

Compound **7** was obtained as a gum, and its molecular formula C<sub>33</sub>H<sub>40</sub>O<sub>14</sub> was indicated by HRESIMS. The IR spectrum of **7** displayed absorption bands for OH (3426 cm<sup>-1</sup>) and aromatic ring (1608 and 1514 cm<sup>-1</sup>) groups. The <sup>1</sup>H NMR spectrum of **7** showed signals due to two 1,3,4-trisubstituted phenyl groups, a 1,3,4,5-tetrasubstituted phenyl group, and three methoxy groups. In addition, it showed signals attributed to three oxymethine protons at δ 5.46 (H-7), 4.83 (H-7'), and 4.87 (H-1''), partially overlapped methylene and methine protons between δ 3.14 and 3.70, and broad signals due to eight OH protons between δ 4.10 and 5.30. In addition to carbon resonances corresponding to the above units, the <sup>13</sup>C NMR and DEPT spectra of **7** displayed carbon signals attributed to two oxymethines at δ 86.5 (C-7) and 72.5 (C-7'), two oxymethylenes at δ 63.4 (C-9) and 62.6 (C-9'), and two aliphatic methines at δ 53.5 (C-8) and 55.2 (C-8'). These spectroscopic data suggested that **7** was a dihydro[*b*]benzofuran neolignan glycoside with an additional tri- or disubstituted aryl group.<sup>22</sup> Enzymatic hydrolysis of **7** produced D-glucose and **7a**, and the <sup>1</sup>H NMR data of **7a** were in agreement with those of leptolepisol C isolated from *Larix leptolepis*.<sup>23</sup> This indicated that **7** was leptolepisol C β-D-glucoside, which was confirmed by HMQC and HMBC experiments of **7**. In the HMBC spectrum, a correlation from the anomeric proton to C-4 indicated unequivocally that the β-glucopyranosyl moiety was located at C-4. Consequently, **7** was determined to be leptolepisol C 4-*O*-β-D-glucopyranoside. The CD spectra of **7** and **7a** did not give any useful Cotton effect due to interaction among three aromatic rings, and the absolute configuration of **7** and **7a** remains to be determined.

Compound **8** showed IR absorption bands for OH (3374 cm<sup>-1</sup>) and aromatic (1612 and 1513 cm<sup>-1</sup>) functional groups. The ESIMS of **8** gave [M + Na]<sup>+</sup> and [M + K]<sup>+</sup> peaks at *m/z* 429 and 445. The <sup>1</sup>H NMR spectrum of **8** in DMSO-*d*<sub>6</sub> showed a two-proton aromatic singlet at δ 6.64, a six-proton methoxy singlet at δ 3.75, two deshielded oxymethine doublets at δ 4.63 (H-7) and 4.25 (H-1'), and partially overlapped oxymethylene and/or oxymethine multiplets integrated for nine protons between δ 3.00 and 3.75

**Table 3.** NMR Data for Compounds **8** and **9**<sup>a</sup>

no.	<b>8</b>		<b>9</b>	
	H	C	H	C
1		131.9		132.7
2	6.64 s	104.6	6.97 d (1.2)	111.5
3		147.4		147.0
4		134.3		145.4
5		147.4	6.67 d (8.0)	114.6
6	6.64 s	104.6	6.73 dd (8.0, 1.2)	119.4
7	4.63 d (4.4)	72.6	4.63 d (4.0)	72.5
8	3.75 m	84.6	3.72 m	84.9
9a	3.42 dd (11.2, 4.4)	61.1	3.39 dd (11.2, 5.2)	61.1
9b	3.29 dd (11.2, 4.8)		3.25 dd (11.2, 4.8)	
1'	4.25 d (8.0)	103.1	4.26 d (7.6)	103.3
2'	3.00 dd (8.8, 8.0)	73.8	3.00 dd (8.8, 7.6)	73.9
3'	3.10 dd (8.8, 8.8)	76.4	3.13 dd (8.8, 8.8)	76.4
4'	3.02 dd (8.8, 8.8)	70.1	3.02 dd (8.8, 8.4)	70.1
5'	3.10 m	76.9	3.10 m	76.9
6'a	3.66 dd (11.6, 1.6)	61.0	3.64 brd (12.0)	61.0
6'b	3.38 dd (11.6, 5.2)		3.39 (12.0, 6.4)	
OMe	3.73 s	55.9	3.74 s	55.6

<sup>a</sup> <sup>1</sup>H NMR data ( $\delta$ ) were measured in DMSO-*d*<sub>6</sub> at 400 MHz. Proton coupling constants (*J*) in Hz are given in parentheses. <sup>13</sup>C NMR data ( $\delta$ ) were measured in DMSO-*d*<sub>6</sub> at 125 MHz.

(Table 3). The <sup>13</sup>C NMR and DEPT spectra of **8** displayed characteristic signals for 1-*C*-syringylglycerol and  $\beta$ -glucopyranosyl moieties (Table 3). Enzymatic hydrolysis of **8** with  $\beta$ -glucosidase yielded **8a** with  $[\alpha]_D -19.6$  (*c* 0.25, MeOH) and D-glucose. The NMR data of **8a** (Tables S11 and S13) were in good agreement with those of *erythro*-1-*C*-syringylglycerol,<sup>24,25</sup> indicating that it was (–)-*erythro*-1-*C*-syringylglycerol  $\beta$ -D-glucopyranoside. Comparison of the NMR data of **8** and **8a** indicated that C-8 of **8** was significantly deshielded by  $\Delta\delta$  9.3 ppm. This suggested that the  $\beta$ -D-glucopyranosyl moiety was located at C-8 of (–)-*erythro*-syringylglycerol in **8**. Since *erythro*-aryl glycerols with 7*R*,8*S* configuration were reported to have negative  $[\alpha]_D$  values,<sup>26,27</sup> the absolute configuration at C-7 and C-8 of **8a** was assigned as 7*R*,8*S*. Thus, the structure of **8** was determined to be (–)-(7*R*,8*S*)-syringylglycerol 8-*O*- $\beta$ -D-glucopyranoside.

Compound **9** gave  $[M + Na]^+$  and  $[M + K]^+$  peaks at *m/z* 399 and 415 in the positive ESIMS. The IR and NMR data were similar to those of **8** except that the syringyl unit in **8** was replaced by a guaiacyl unit in **9**. This suggested that **9** was a demethoxy derivative of **8**. Hydrolysis of **9** yielded **9a**, with  $[\alpha]_D -12.4$  (*c* 0.33, MeOH), and D-glucose. The NMR data of **9a** (Tables S12 and S13) were identical to those of (7*S*,8*R*)-guaiacylglycerol except for an opposite optical rotation ( $[\alpha]_D +11$ ).<sup>8,27</sup> Therefore, **9** was determined to be (–)-(7*R*,8*S*)-guaiacylglycerol 8-*O*- $\beta$ -D-glucopyranoside.

The known compounds were identified by comparison of spectroscopic data with those reported in the literature as (–)-(7*R*,8*S*,7*E*)-4,7,9,9'-tetrahydroxy-3,3'-dimethoxy-8-4'-oxyneolign-7'-ene-9'-*O*- $\beta$ -D-glucopyranoside (hyuganose IIIa, **10**),<sup>11</sup> (–)-(7*S*,8*S*,7*E*)-4,7,9,9'-tetrahydroxy-3,3'-dimethoxy-8-4'-oxyneolign-7'-ene-9'-*O*- $\beta$ -D-glucopyranoside (hyuganose IIIb, **11**),<sup>11</sup> (+)-(7*S*,8*S*)-syringylglycerol 8-*O*- $\beta$ -D-glucopyranoside (**12**),<sup>7</sup> (+)-(7*S*,8*S*)-guaiacylglycerol 8-*O*- $\beta$ -D-glucopyranoside (**13**),<sup>30</sup> (–)-(7*S*,8*R*)-guaiacylglycerol 9-*O*- $\beta$ -D-glucopyranoside (**14**),<sup>8</sup> (–)-(7*R*,8*R*)-guaiacylglycerol 9-*O*- $\beta$ -D-glucopyranoside (**15**),<sup>8</sup> (–)-(7*R*,8*R*)-syringylglycerol 9-*O*- $\beta$ -D-glucopyranoside (**16**),<sup>31</sup> (–)-(7*R*,8*R*)-guaiacylglycerol 7-*O*- $\beta$ -D-glucopyranoside,<sup>32</sup> (–)-tachioside,<sup>33</sup> (–)-liriodendrin (**17**),<sup>34</sup> (–)-sweroside,<sup>35</sup> (–)-11,13-dihydrodeacetylcynaropicrin 3-*O*- $\beta$ -D-glucopyranoside,<sup>36</sup> (–)-3,5-dimethoxy-4-hydroxyphenyl  $\beta$ -D-glucopyranoside (incorrect nomenclature was given in the literature<sup>37</sup>), (–)-(1'*R*)-1-(3-hydroxy-4-methoxyphenyl)ethane-1',2'-diol 3-*O*- $\beta$ -D-glucopyranoside,<sup>38</sup> (–)-3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone 3-*O*- $\beta$ -D-glucopyranoside,<sup>39</sup> (–)-2-hydroxy-5-(2-hydroxyethyl)phenyl  $\beta$ -D-glucopyranoside,<sup>32</sup> (–)-2-methoxy-4-(1-propionyl)phenyl  $\beta$ -D-glucopyranoside,<sup>40</sup> and (–)-4-propionyl-2,6-dimethoxyphenyl  $\beta$ -D-glucopyranoside.<sup>41</sup> The absolute configurations of **10**, **11**, and **12** were determined on the basis of CD

spectra and/or optical rotations of their aglycones, and **13** was obtained as a natural product for the first time.

Coupling constants (*J*<sub>7,8</sub>) of the deshielded benzylic proton (H-7) signal in the <sup>1</sup>H NMR spectra of the acetates of *erythro* (*J*<sub>7,8</sub> ≤ 5.3 Hz) and *threo* (*J*<sub>7,8</sub> ≥ 6.3 Hz) 8-4'-oxyneolignan aglycones and glycosides,<sup>12,18</sup> as well as acetone derivatives of *threo* (*J*<sub>7,8</sub> < 2.0 Hz) and *erythro* (*J*<sub>7,8</sub> > 8.0 Hz) 8-4'-oxyneolignan aglycones,<sup>11,17</sup> unambiguously distinguished *erythro* and *threo* isomers in CDCl<sub>3</sub>. However, there were several cases where the values of *J*<sub>7,8</sub> of 8-4'-oxyneolignans were directly applied for the differentiation of *erythro* and *threo* isomers without derivatization.<sup>5,6,14a,15,42</sup> A systematic analysis of <sup>1</sup>H NMR data of **1–5** in DMSO-*d*<sub>6</sub> (Table 1) and **1a–5a**, **10a**, **11a**, **5**, **10**, and **11** in different solvents (Tables S1–S5, Supporting Information), in combination with the data of 8-4'-oxyneolignan derivatives in the literature,<sup>11–15,17,44</sup> indicated that the values of *J*<sub>7,8</sub> were variable in different solvents due to possible dynamic conformational changes.<sup>43</sup> In Me<sub>2</sub>CO-*d*<sub>6</sub> + D<sub>2</sub>O or CDCl<sub>3</sub>, the *J*<sub>7,8</sub> values of the *threo* 8-4'-oxyneolignan aglycones **5a** and **11a** (6.0 and 6.6 Hz in Me<sub>2</sub>CO-*d*<sub>6</sub> + D<sub>2</sub>O and 8.4 and 8.4 Hz in CDCl<sub>3</sub>, respectively) were larger than those of the *erythro* analogues **1a**, **2a** (**4a**), **3a**, and **10a** (4.8, 4.8, 3.0, and 5.4 Hz in Me<sub>2</sub>CO-*d*<sub>6</sub> + D<sub>2</sub>O and 4.2, 3.6, 4.2, and 4.2 Hz in CDCl<sub>3</sub>, respectively). Meanwhile, in C<sub>3</sub>D<sub>5</sub>N, the *J*<sub>7,8</sub> values of the glycosides **5** and **11** (6.0 and 5.4 Hz) were larger than that of the *erythro* analogue **10** (4.8 Hz). However, in CD<sub>3</sub>OD, the *J*<sub>7,8</sub> values of the *threo* aglycones **5a** and **11a** (6.0 and 5.4 Hz) were smaller than or equal to the *erythro* aglycones **10a** (6.0 Hz), and in DMSO-*d*<sub>6</sub>, D<sub>2</sub>O, and CD<sub>3</sub>OD, the *J*<sub>7,8</sub> values of *threo* glycosides **5** and **11** were smaller than or equal to those of the *erythro* glycosides. In addition, it was clear that the differences of the *J*<sub>7,8</sub> values between *threo* and *erythro* aglycones in Me<sub>2</sub>CO-*d*<sub>6</sub> + D<sub>2</sub>O and glycosides in C<sub>3</sub>D<sub>5</sub>N are small and close to the range of NMR instrument errors. Therefore, the direct application of the *J*<sub>7,8</sub> values was ambiguous to differentiate *erythro* and *threo* 8-4'-oxyneolignans with the exception of aglycone acetones (*J*<sub>7,8</sub> > 8.0 Hz for *erythro*, and *J*<sub>7,8</sub> < 2.0 Hz for *threo*) and glycoside acetates (*J*<sub>7,8</sub> ≤ 5.3 Hz for *erythro*, and *J*<sub>7,8</sub> ≥ 6.3 Hz for *threo*) in CDCl<sub>3</sub>, as well as aglycones in CDCl<sub>3</sub> (*J*<sub>7,8</sub> ≤ 5.0 Hz for *erythro*, and *J*<sub>7,8</sub> ≥ 8.0 Hz for *threo*).

In order to evaluate a possible application of the <sup>13</sup>C NMR spectroscopic data for distinguishing *erythro* and *threo* 8-4'-oxyneolignan derivatives, the <sup>13</sup>C NMR data of **1–5** in DMSO-*d*<sub>6</sub> (Table 2) and **1a**, **2a** (**4a**), **5a**, **10a**, **11a**, **2**, **5**, **10**, and **11** in different solvents (Tables S6 and S7, Supporting Information), together with



the data of 8-4'-oxyneolignan derivatives in the literature,<sup>11,15,17,44a</sup> were investigated. The chemical shift difference between C-8 and C-7 ( $\Delta\delta_{C8-C7}$ ) was used in the discussion to eliminate the systematic errors. The  $\Delta\delta_{C8-C7}$  values of the *erythro* and *threo* isomers (**10** and **11**, and **10a** and **11a**) were variable in different solvents. In DMSO-*d*<sub>6</sub>, C<sub>5</sub>D<sub>5</sub>N, or CD<sub>3</sub>OD, the  $\Delta\delta_{C8-C7}$  values of the *erythro* glycoside **10** (12.1, 12.6, or 12.1 ppm) were smaller than those of the *threo* isomer **11** (13.4, 13.9, or 13.1 ppm). Meanwhile, in Me<sub>2</sub>CO-*d*<sub>6</sub>, CD<sub>3</sub>OD, or CDCl<sub>3</sub>, the  $\Delta\delta_{C8-C7}$  values of the *erythro* aglycone **10a** (12.9, 12.1, or 14.6 ppm) were smaller than those of the *threo* isomer **11a** (14.7, 13.2, or 15.5 ppm). These were fully consistent with data reported in the literature.<sup>11,15,17,44a</sup> However, in D<sub>2</sub>O the  $\Delta\delta_{C8-C7}$  value of the *erythro* glycoside **10** (11.0 ppm) was larger than that of the *threo* isomer **11** (10.7 ppm), and in CD<sub>3</sub>OD the  $\Delta\delta_{C8-C7}$  value of the *erythro* glycoside **2** (13.7 ppm) was larger than that of its *threo* isomer (12.9 ppm).<sup>15</sup> In the same solvent, the  $\Delta\delta_{C8-C7}$  values of the 8-4'-oxyneolignan analogues [**1–5**, **1a**, **2a** (**4a**), and **10a**] were variable due to substituent differences at C-3' and/or C-5'. Therefore, the  $\Delta\delta_{C8-C7}$  values may be useful to distinguish the *erythro* and *threo* 8-4'-oxyneolignan isomers when the data are obtained in the same solvent.

The  $J_{7,8}$  values of arylglycerol acetates were used to distinguish *threo*- ( $J_{7,8} > 7.0$  Hz) and *erythro*- ( $J_{7,8} < 6.5$  Hz) arylglycerols,<sup>29,30,44b,45</sup> and our previous investigation indicated that the chemical shift difference of C-7 and C-8 ( $\Delta\delta_{C8-C7}$ ) was also applicable to differentiate *threo*- and *erythro*-aryl glycerols without substituent(s) at C-7 and/or C-8 of the glycerol moiety.<sup>25</sup> A systematic analysis of the NMR data of **8**, **9**, **12**, and **13** in D<sub>2</sub>O, DMSO-*d*<sub>6</sub>, C<sub>5</sub>D<sub>5</sub>N, or CD<sub>3</sub>OD (Tables S8–S10, Supporting Information) and the data of *erythro*- and *threo*-aryl glycerol 8-*O*- $\beta$ -D-glucopyranosides in the literature<sup>7–9,29–31</sup> (the relative configurations at C-7 and C-8 were wrongly assigned in ref 9) indicated that the values of both  $J_{7,8}$  and  $\Delta\delta_{C8-C7}$  were variable in different solvents. However, in DMSO-*d*<sub>6</sub>, C<sub>5</sub>D<sub>5</sub>N, or CD<sub>3</sub>OD except for D<sub>2</sub>O, the differences of  $J_{7,8}$  and  $\Delta\delta_{C8-C7}$  between *erythro*- and *threo*-aryl glycerol 8-*O*- $\beta$ -D-glucopyranosides were significant and may be directly applicable to distinguish *erythro*- ( $J_{7,8} \leq 4.4$  Hz in DMSO-*d*<sub>6</sub>, C<sub>5</sub>D<sub>5</sub>N, or CD<sub>3</sub>OD,  $\Delta\delta_{C8-C7} \leq 12.5$  ppm in DMSO-*d*<sub>6</sub> or C<sub>5</sub>D<sub>5</sub>N, and  $\Delta\delta_{C8-C7} < 11.0$  ppm in CD<sub>3</sub>OD) and *threo*-aryl glycerol 8-*O*- $\beta$ -D-glucopyranosides ( $J_{7,8} \geq 6.0$  Hz in DMSO-*d*<sub>6</sub>, C<sub>5</sub>D<sub>5</sub>N, or CD<sub>3</sub>OD,  $\Delta\delta_{C8-C7} \geq 14.0$  ppm in DMSO-*d*<sub>6</sub> or C<sub>5</sub>D<sub>5</sub>N, and  $\Delta\delta_{C8-C7} > 12.0$  ppm in CD<sub>3</sub>OD). The  $\Delta\delta_{C8-C7}$  of the aglycones **8a**, **9a**, **12a**, and **13a** in Me<sub>2</sub>CO-*d*<sub>6</sub>, CD<sub>3</sub>OD, C<sub>5</sub>D<sub>5</sub>N, and DMSO-*d*<sub>6</sub> were consistent with those of our previously reported data for *erythro*- ( $\Delta\delta_{C8-C7} < 1.0$  ppm in Me<sub>2</sub>CO-*d*<sub>6</sub>, CD<sub>3</sub>OD, or C<sub>5</sub>D<sub>5</sub>N, and  $\Delta\delta_{C8-C7} \leq 1.4$  in DMSO-*d*<sub>6</sub>) and *threo*- ( $\Delta\delta_{C8-C7} \geq 2.0$  ppm in all tested solvents) arylglycerols without substituent(s) at C-7 and/or C-8,<sup>25</sup> although the values of  $J_{7,8}$  were indistinguishable among the aglycones without substituent(s) at C-7 and/or C-8 (Tables S11–S13). In addition, an investigation of the NMR data of three known *erythro*- and *threo*-aryl glycerol 9-*O*- $\beta$ -D-glucopyranosides (**14–16**) (Tables S14 and S15, Supporting Information) in different solvents, together with the data of *erythro*- and *threo*-aryl glycerol 9-*O*- $\beta$ -D-glucopyranosides<sup>7–9,28,31</sup> (the relative configurations at C-7 and C-8 were wrongly assigned in refs 7 and 9) indicated that there was no significant difference among  $J_{7,8}$  values of *erythro*- and *threo*-aryl glycerol 9-*O*- $\beta$ -D-glucopyranosides. However, in DMSO-*d*<sub>6</sub> or C<sub>5</sub>D<sub>5</sub>N except for in D<sub>2</sub>O or CD<sub>3</sub>OD  $\Delta\delta_{C8-C7}$  values are applicable to distinguish *erythro*- ( $\Delta\delta_{C8-C7} \leq 0.5$  ppm in DMSO-*d*<sub>6</sub> or C<sub>5</sub>D<sub>5</sub>N) and *threo*- ( $\Delta\delta_{C8-C7} > 1.0$  ppm in DMSO-*d*<sub>6</sub> or C<sub>5</sub>D<sub>5</sub>N) arylglycerol 9-*O*- $\beta$ -D-glucopyranosides.

The neuroprotective activity of the purified compounds against glutamate-induced neurotoxicity in cultures of PC12 cells was evaluated by the MTT assay. As shown in Table 4, treatment with glutamate (20  $\mu$ M) resulted in significant inhibition of MTT reduction. However, exposure of compounds **4** and **17** at the concentration of 10<sup>-5</sup> M for 24 h remarkably attenuated glutamate-

**Table 4.** Activities of Selected Compounds to Glutamate-Induced Neurotoxicity in PC12 Cells<sup>a</sup>

compound	relative protection (%)
control	100 $\pm$ 1.9
glutamate-treated	0.0 $\pm$ 2.8 <sup>#</sup>
NGF	108.2 $\pm$ 2.1**
<b>4</b>	36.4 $\pm$ 3.1*
<b>9</b>	-46.6 $\pm$ 2.2**
<b>12</b>	-28.4 $\pm$ 1.9**
<b>13</b>	-32.9 $\pm$ 1.9**
<b>17</b>	20.5 $\pm$ 1.8**

<sup>a</sup> The data are expressed as mean  $\pm$  SD of three independent experiments. (<sup>#</sup>*p* < 0.05 vs control; \**p* < 0.05, \*\**p* < 0.01 vs glutamate-treated group).

induced cytotoxicity, whereas, **11–13** increased the cell damage. The other compounds were all inactive.

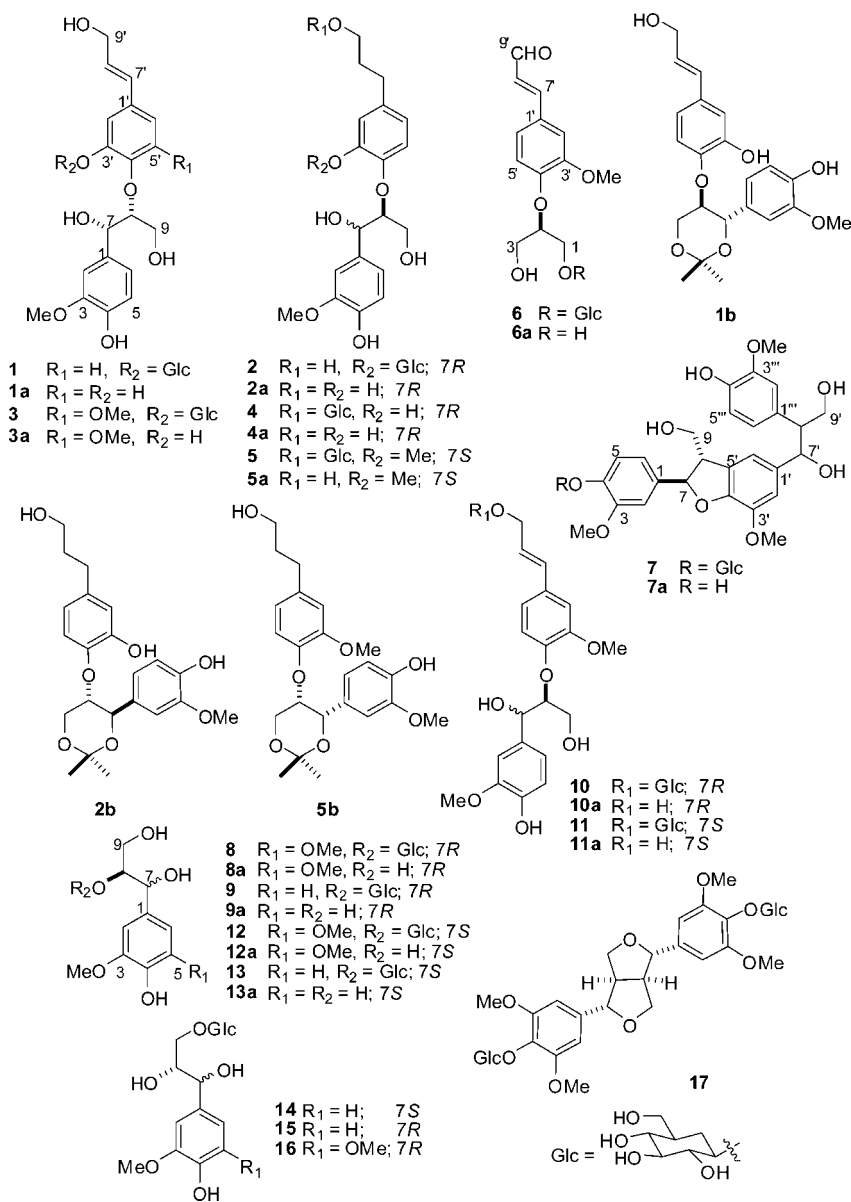
## Experimental Section

**General Experimental Procedures.** Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter. UV spectra were measured on a Cary 300 spectrophotometer. CD spectra were recorded on a JASCO J-810 spectropolarimeter. IR spectra were recorded as KBr disks on a Nicolet 5700 FT-IR instrument. NMR spectra were obtained at 400, 500, or 600 MHz for <sup>1</sup>H and 100, 125, or 150 MHz for <sup>13</sup>C, respectively, on Inova 400, 500, and 600 MHz spectrometers in DMSO-*d*<sub>6</sub>, C<sub>5</sub>D<sub>5</sub>N, CD<sub>3</sub>OD, Me<sub>2</sub>CO-*d*<sub>6</sub>, D<sub>2</sub>O, or CDCl<sub>3</sub> with solvent peaks (or TMS, in the case of D<sub>2</sub>O) used as references. ESIMS data were measured with a Q-Trap LC/MS/MS (Turbo Ionspray Source) spectrometer. HRFABMS and HRESIMS data were respectively measured using a Micromass Autospec-Ultima ETOF and an AccuToFCS JMS-T100CS spectrometer. Column chromatography (CC) was performed with silica gel (200–300 mesh, Qingdao Marine Chemical Inc. China) and Sephadex LH-20 (Pharmacia Biotech AB, Uppsala Sweden). HPLC separation was performed on an instrument consisting of a Waters 600 controller, a Waters 600 pump, and a Waters 2487 dual  $\lambda$  absorbance detector with an Alltima (250  $\times$  10 mm i.d.) preparative column packed with C<sub>18</sub> (5  $\mu$ M). TLC was carried out with glass precoated silica gel GF<sub>254</sub> plates. Spots were visualized under UV light or by spraying with 7% H<sub>2</sub>SO<sub>4</sub> in 95% EtOH followed by heating.

**Plant Material.** The root of *I. cirrhosa* (6.0 kg) was collected at Dayao Mountain, Guangxi Province, China, in August 2002. The plant was identified by Mr. Guang-Ri Long (Guangxi Forest Administration, Guangxi 545005, China). A voucher specimen (no. YG02011) was deposited at the Herbarium of the Department of Medicinal Plants, Institute of Materia Medica, Beijing, China.

**Extraction and Isolation.** The air-dried root of *I. cirrhosa* (6 kg) was powdered and extracted with 95% EtOH (3  $\times$  15 L) at room temperature for 3  $\times$  48 h. The ethanolic extract was evaporated under reduced pressure to yield a dark brown residue (640 g). The residue was suspended in H<sub>2</sub>O (2000 mL) and then partitioned with EtOAc (5  $\times$  2000 mL). The aqueous phase was applied to a HDP100 macroporous adsorbent resin (1000 g, dried weight) column. A successive elution of the column with H<sub>2</sub>O, 30% EtOH, 60% EtOH, and 95% EtOH (5000 mL each) yielded four corresponding portions after removing solvents. The portion (24.0 g) eluted by 30% EtOH was separated by MPLC over reversed-phase silica gel eluting with a gradient of increasing MeOH (0–60%) in H<sub>2</sub>O to give four fractions (A–D) on the basis of TLC analysis. Subsequent separation of fraction A (7.5g) over Sephadex LH-20 eluted with H<sub>2</sub>O gave four subfractions (A<sub>1</sub>–A<sub>4</sub>). Subfraction A<sub>2</sub> (0.98 g) was further fractionated via silica gel CC, eluting with CHCl<sub>3</sub>–MeOH (8:1), to yield two fractions (A<sub>2-1</sub>, A<sub>2-2</sub>). Fraction A<sub>2-1</sub> (0.31 g) was subjected to reversed-phase preparative HPLC, using a mobile phase of MeOH–H<sub>2</sub>O–HOAc (6.5:93.5:0.5), to afford **8** (110 mg), **9** (51 mg), **12** (15 mg), and **13** (15 mg). Fraction B (13.0 g) was separated by normal silica gel CC, eluting with a gradient of increasing MeOH (10–50%) in CHCl<sub>3</sub>, to afford five fractions (B<sub>1</sub>–B<sub>5</sub>). B<sub>1</sub> (4.60 g) was further separated into five subfractions (B<sub>1-1</sub>–B<sub>1-5</sub>) by reversed-phase flash chromatography using step-gradient elution with increasing MeOH (0–30%) in H<sub>2</sub>O. Fraction B<sub>1-2</sub> (0.68 g) was subjected to CC over Sephadex LH-20, eluting with H<sub>2</sub>O, to give four mixtures (B<sub>1-2-1</sub>–B<sub>1-2-4</sub>). B<sub>1-2-2</sub> (96 mg) was purified by reversed-phase prepara-

Chart 1



tive HPLC using the mobile phase of MeCN–H<sub>2</sub>O–HOAc (10:90:0.5) to afford **6** (16 mg). Fraction B<sub>1–2–3</sub> (54 mg) was separated by reversed-phase preparative HPLC using MeOH–H<sub>2</sub>O–HOAc (21:79:0.5) to yield **1** (13 mg) and **2** (15 mg). B<sub>1–4</sub> (0.75 g) was subjected to CC over Sephadex LH-20 with H<sub>2</sub>O as eluent to give four mixtures (B<sub>1–4–1</sub>–B<sub>1–4–4</sub>). Fraction B<sub>1–4–3</sub> (243 mg) was separated by reversed-phase preparative HPLC with the mobile phase MeOH–H<sub>2</sub>O (30:70) to yield **3** (10 mg), **4** (12 mg), **5** (26 mg), **7** (11 mg), **10** (17 mg), and **11** (21 mg).

(–)-(7*S*,8*R*,7′*E*)-4,7,9,3′,9′-Pentahydroxy-3-methoxy-8-4′-oxyneolignan-7′-ene-3′-O-β-D-glucopyranoside (**1**): amorphous solid;  $[\alpha]_D^{20} -6.2$  (*c* 0.08, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 205 (4.3), 261 (3.9) nm; CD (MeOH) 221 ( $\Delta\epsilon -0.82$ ), 233 ( $\Delta\epsilon -2.08$ ), 250 ( $\Delta\epsilon +0.07$ ) nm; IR (KBr)  $\nu_{\text{max}}$  3358, 2920, 1602, 1509, 1453, 1267, 1072, 1024  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz) data, see Table 1; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz) data, see Table 2; ESIMS *m/z* 547 [M + Na]<sup>+</sup> and 563 [M + K]<sup>+</sup>; HRFABMS *m/z* 547.1801 [M + Na]<sup>+</sup> (calcd for C<sub>25</sub>H<sub>32</sub>O<sub>12</sub>Na, 547.1791).

(–)-(7*R*,8*S*)-4,7,9,3′,9′-Pentahydroxy-3-methoxy-8-4′-oxyneolignan-3′-O-β-D-glucopyranoside (**2**): amorphous powder;  $[\alpha]_D^{20} -17.6$  (*c* 0.45, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 207 (4.4), 278 (3.6) nm; CD (MeOH) 228 ( $\Delta\epsilon -2.34$ ), 237 ( $\Delta\epsilon +1.54$ ), 244 ( $\Delta\epsilon -0.18$ ) nm; IR (KBr)  $\nu_{\text{max}}$  3381, 1604, 1509, 1270, 1026  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz) data, see Table 1; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz) data,

see Table 2; ESIMS *m/z* 549 [M + Na]<sup>+</sup> and 565 [M + K]<sup>+</sup>; HRESIMS *m/z* 549.1963 [M + Na]<sup>+</sup> (calcd for C<sub>25</sub>H<sub>34</sub>O<sub>12</sub>Na 549.1948).

(–)-(7*S*,8*R*,7′*E*)-4,7,9,3′,9′-Pentahydroxy-3,5′-dimethoxy-8-4′-oxyneolignan-7′-ene-3′-O-β-D-glucopyranoside (**3**): amorphous powder;  $[\alpha]_D^{20} -9.0$  (*c* 0.10, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 204 (4.3), 221 (4.2), 269 (3.8) nm; CD (MeOH) 226 ( $\Delta\epsilon -0.46$ ), 235 ( $\Delta\epsilon -2.84$ ), 250 ( $\Delta\epsilon +0.72$ ) nm; IR (KBr)  $\nu_{\text{max}}$  3422, 1590, 1508, 1076, 1037  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz) data, see Table 1; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz) data, see Table 2; ESIMS *m/z* 577 [M + Na]<sup>+</sup>, 593 [M + K]<sup>+</sup>, and 553 [M – H]<sup>–</sup>; HRESIMS *m/z* 577.1851, [M + Na]<sup>+</sup> (calcd for C<sub>26</sub>H<sub>34</sub>O<sub>13</sub>Na 577.1897).

(–)-(7*R*,8*S*)-4,7,9,3′,9′-Pentahydroxy-3-methoxy-8-4′-oxyneolignan-9′-O-β-D-glucopyranoside (**4**): colorless gum;  $[\alpha]_D^{20} -12.5$  (*c* 0.08, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 207 (4.4), 280 (3.7) nm; CD (MeOH) 226 ( $\Delta\epsilon -1.52$ ), 238 ( $\Delta\epsilon +1.14$ ), 250 ( $\Delta\epsilon -0.12$ ) nm; IR (KBr)  $\nu_{\text{max}}$  3413, 1604, 1512, 1277, 1030  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz) data, see Table 1; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz) data, see Table 2; ESIMS *m/z* 549 [M + Na]<sup>+</sup>, 565 [M + K]<sup>+</sup>, and 525 [M – H]<sup>–</sup>; HRESIMS *m/z* 549.1963 [M + Na]<sup>+</sup> (calcd for C<sub>25</sub>H<sub>34</sub>O<sub>12</sub>Na 549.1948).

(+)-(7*S*,8*S*)-4,7,9,9′-Tetrahydroxy-3,3′-dimethoxy-8-4′-oxyneolignan-9′-O-β-D-glucopyranoside (**5**): amorphous solid;  $[\alpha]_D^{20} +2.0$  (*c* 1.20, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 230 (4.1), 280 (3.4) nm; CD (MeOH) 226 ( $\Delta\epsilon +0.48$ ), 236 ( $\Delta\epsilon +1.75$ ), 250 ( $\Delta\epsilon +0.15$ ); IR (KBr)  $\nu_{\text{max}}$  3283,

1558, 1513, 1259, 1032  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 500 MHz) data, see Table 1;  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz) data, see Table 2; ESIMS  $m/z$  563  $[\text{M} + \text{Na}]^+$  and 539  $[\text{M} - \text{H}]^-$ ; HRESIMS  $m/z$  563.2097  $[\text{M} + \text{Na}]^+$  (calcd for  $\text{C}_{26}\text{H}_{34}\text{O}_{12}\text{Na}$  563.2104).

(-)-(2R)-1-O- $\beta$ -D-Glucopyranosyl-2-(2-methoxy-4-(E)-formylvinyl)phenoxy]propane-3-ol (6): yellowish, amorphous powder;  $[\alpha]_D^{20}$   $-7.5$  (c 0.08, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 202 (4.4), 224 (4.3), 237 (4.3), 334 (4.5) nm; IR (KBr)  $\nu_{\text{max}}$  3379, 2921, 1662, 1595, 1511, 1272, 1137, 1078  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz) data, see Table 1;  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz) data, see Table 2; ESIMS  $m/z$  437  $[\text{M} + \text{Na}]^+$  and 453  $[\text{M} + \text{K}]^+$ ; HRFABMS  $m/z$  437.1406  $[\text{M} + \text{Na}]^+$  (calcd for  $\text{C}_{19}\text{H}_{26}\text{O}_{10}\text{Na}$ , 437.1424).

Leptolepisol C 4-O- $\beta$ -D-glucopyranoside (7): colorless gum;  $[\alpha]_D^{20}$   $-6.0$  (c 0.10, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 208 (4.8), 279 (4.0) nm; IR (KBr)  $\nu_{\text{max}}$  3426, 1608, 1514, 1268, 1030  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 500 MHz) data, see Table 1;  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz) data, see Table 2; ESIMS  $m/z$  683  $[\text{M} + \text{Na}]^+$ , 699  $[\text{M} + \text{K}]^+$ , and 659  $[\text{M} - \text{H}]^-$ ; HRESIMS  $m/z$  683.2338  $[\text{M} + \text{Na}]^+$  (calcd for  $\text{C}_{33}\text{H}_{40}\text{O}_{14}\text{Na}$  683.2316).

(-)-(7R,8S)-Syringylglycerol 8-O- $\beta$ -D-glucopyranoside (8): white, amorphous powder;  $[\alpha]_D^{20}$   $-14.3$  (c 0.30, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 211 (4.2), 232 (3.7), 271 (3.4) nm; IR (KBr)  $\nu_{\text{max}}$  3374, 1612, 1513, 1228, 1073, 1043  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz) and  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz) data, see Table 3; ESIMS  $m/z$  429  $[\text{M} + \text{Na}]^+$  and 445  $[\text{M} + \text{K}]^+$ .

(-)-(7R,8S)-Guaiacylglycerol 8-O- $\beta$ -D-glucopyranoside (9): white, amorphous powder;  $[\alpha]_D^{20}$   $-21.5$  (c 0.55, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 230 (3.8), 278 (3.2) nm; IR (KBr)  $\nu_{\text{max}}$  3383, 1605, 1517, 1272, 1073, 1028  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz) and  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz) data, see Table 3; ESIMS  $m/z$  399  $[\text{M} + \text{Na}]^+$  and 415  $[\text{M} + \text{K}]^+$ .

**Enzymatic Hydrolysis of 1–13.** A solution of each compound in  $\text{H}_2\text{O}$  (3 mL) was individually hydrolyzed with  $\beta$ -glucosidase (10 mg, Almonds Lot 1264252, Sigma-Aldrich) at 37 °C for 24 or 36 h. Each reaction mixture was extracted with EtOAc (3  $\times$  3 mL) to yield the individual EtOAc extract and  $\text{H}_2\text{O}$  phase after removing the solvents.

The EtOAc extracts were separately chromatographed over silica gel, eluting with  $\text{CH}_2\text{Cl}_2$ –MeOH (12:1) for the hydrolysates from 1–7 (3–12 mg), 10 (6 mg), and 11 (11 mg) to yield aglycones 1a–7a, 10a, and 11a, respectively, and eluting with  $\text{CH}_2\text{Cl}_2$ –MeOH (10:1) for the hydrolysates from 8, 9, 12, and 13 (each 10 mg) to yield 8a, 9a, 12a, and 13a.

Compound 1a (2.0 mg):  $[\alpha]_D^{20}$   $+1.5$  (c 0.20, MeOH), CD (MeOH) 236 ( $\Delta\epsilon$   $-1.26$ ); 2a (2.1 mg):  $[\alpha]_D^{20}$   $-7.9$  (c 0.21, MeOH), CD (MeOH) 238 ( $\Delta\epsilon$   $+1.46$ ); 3a (1.4 mg):  $[\alpha]_D^{20}$   $-2.8$  (c 0.14, MeOH), CD (MeOH) 236 ( $\Delta\epsilon$   $-0.58$ ); 4a (1.8 mg):  $[\alpha]_D^{20}$   $-4.2$  (c 0.18, MeOH), CD (MeOH) 238 ( $\Delta\epsilon$   $+0.58$ ); 5a (7.4 mg):  $[\alpha]_D^{20}$   $+16.9$  (c 0.67, MeOH), CD (MeOH) 235 ( $\Delta\epsilon$   $+2.59$ ); 6a (3.2 mg); 7a (2.2 mg):  $[\alpha]_D^{20}$   $+4.0$  (c 0.22, MeOH); 8a (4.0 mg):  $[\alpha]_D^{20}$   $-19.6$  (c 0.25, MeOH); 9a (4.0 mg):  $[\alpha]_D^{20}$   $-12.4$  (c 0.33, MeOH); 10a (2.1 mg):  $[\alpha]_D^{20}$   $-4.0$  (c 0.21, MeOH), CD (MeOH) 236 ( $\Delta\epsilon$   $+0.50$ ); 11a (3.8 mg):  $[\alpha]_D^{20}$   $+2.4$  (c 0.38, MeOH), CD (MeOH) 236 ( $\Delta\epsilon$   $+0.58$ ); 12a (4.5 mg):  $[\alpha]_D^{20}$   $+25.1$  (c 0.30, MeOH); 13a (4.5 mg):  $[\alpha]_D^{20}$   $+17.0$  (c 0.30, MeOH).  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR data of 1a–5a and 8a–13a in different solvents, see Tables S1–S3, S6, and S11–S13 in the Supporting Information.  $^1\text{H}$  NMR ( $\text{Me}_2\text{CO}-d_6$ , 600 MHz) and  $^{13}\text{C}$  NMR ( $\text{Me}_2\text{CO}-d_6$ , 150 MHz) data of 6a and 7a were identical with that reported in the literature.<sup>20,23</sup>

The aqueous phases of the hydrolysates of 1–13 were separately subjected to CC over silica gel eluted with  $\text{MeCN}-\text{H}_2\text{O}$  (8:1) to yield glucose with positive optical rotations, and the  $[\alpha]_D^{20}$  values ranged from  $+42.5$  to  $+49.7$  (c in a range of 0.11 to 0.31,  $\text{H}_2\text{O}$ ). The solvent system  $\text{MeCN}-\text{H}_2\text{O}$  (6:1) was used for TLC identification of glucose ( $R_f$ , 0.33).

**Preparation of Acetonide Derivatives (1b, 2b, and 5b).** A solution of 1a (0.8 mg) in dry acetone (1 mL) was treated with 2,2-dimethoxypropane (0.1 mL) and (1S)-(+)-camphorsulfonic acid (CSA) (1 mg, 0.004 mmol), and the mixture was stirred at ambient temperature for 4 h. The reaction mixture was quenched by addition of triethylamine and then evaporated *in vacuo* to give a crude product. The residue was purified by reversed-phase preparative HPLC using  $\text{MeOH}-\text{H}_2\text{O}$  (64:36) to afford acetonide 1b (0.6 mg). Similarly, 2a (1.7 mg) and 5a (2.1 mg) were transformed into acetonide derivatives 2b (1.5 mg) and 5b (1.6 mg), respectively. For  $^1\text{H}$  NMR data (600 MHz) of 1b, 2b, and 5b in  $\text{CDCl}_3$  see Tables S1 and S2 in the Supporting Information.

**Cell Culture and MTT Assay.** PC12 cells at a density of  $5 \times 10^3$  cells per well in 96-well plates were suspended in Dulbecco's modified Eagle's medium (DMEM, Gibco) supplemented with 5% fetal bovine serum (FBS, Hyclone), 5% horse serum, penicillin (100 IU/mL), streptomycin (100  $\mu\text{g}/\text{mL}$ ), and L-glutamine (2  $\mu\text{M}$ ) and incubated in a  $\text{CO}_2$  incubator (5%) at 37 °C for 24 h. Then the cells were pretreated with test compounds ( $10^{-5}$  M) and NGF (50 ng/mL), respectively, for another 24 h before exposed to glutamate (20  $\mu\text{M}$ ). After incubation for an additional 24 h, MTT (0.5 mg/mL) was added to the medium and incubated for 4 h. Absorbance was measured at 570 nm using a microplate reader, and the cell viability was evaluated by relative protection, which was calculated as  $100 \times [\text{optical density (OD) of test compound} + \text{glutamate-treated culture} - \text{OD of glutamated-treated culture}]/[\text{OD of control culture} - \text{OD of glutamated-treated culture}]$ .<sup>46</sup>

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**Supporting Information Available:** Detailed extraction and isolation procedure including known compounds. Figure S1 for HMBC correlation scheme of compounds 1 and 7. Figures S2 and S3 of the CD spectra of compounds 1–5, 10, 11, 1a–5a, 10a, and 11a. 1D NMR spectra of compounds 1–9. Tables S1–S15 of the NMR data for 1a–5a, 8a–13a, 1b, 2b, 5b, 5, and 8–16 in different solvents. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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