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The Constituents of *Eucommia ulmoides* OLIV. I. Isolation of (+)-Medioresinol Di-*O*-β-D-glucopyranoside

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A new lignan diglycoside was isolated from the bark of *Eucommia ulmoides* OLIV. (Eucommiaceae) and its structure was established as (+)-medioresinol di-*O*-β-D-glucopyranoside (**1**) by means of chemical and spectral studies. (+)-Pinoresinol di-*O*-β-D-glucopyranoside (**2**), liriodendrin (**3**) and (+)-pinoresinol *O*-β-D-glucopyranoside (**4**) were also isolated.

Keywords——*Eucommia ulmoides*; lignan; (+)-medioresinol di-*O*-β-D-glucoside; (+)-pinoresinol di-*O*-β-D-glucoside; (+)-pinoresinol *O*-β-D-glucoside; liriodendrin; ^{13}C-NMR

A new lignan glycoside, (+)-medioresinol di-*O*-β-D-glucopyranoside (**1**), was isolated together with three known lignans, (+)-pinoresinol di-*O*-β-D-glucopyranoside (**2**),[1,2] liriodendrin[(+)-syringaresinol di-*O*-β-D-glucopyranoside] (**3**)[3] and (+)-pinoresinol *O*-β-D-glucopyranoside (**4**),[1] from the bark of *Eucommia ulmoides* OLIV. (Japanese name: Tochu) (Eucommiaceae), which is one of the longest-known tonic herbs in China.[4] The extraction and separation were carried out as described in the experimental section.

Glycoside **2** was isolated as a white powder, $C_{32}H_{42}O_{16}$, $[\alpha]_D^{22}$ −24.1° (MeOH), whose molecular weight was observed at *m/z* 705 (M^++Na) and 721 (M^++K) on field desorption-mass spectrometry (FD-MS). Glycoside **2** was identified as (+)-pinoresinol di-*O*-β-D-glucopyranoside[1,2] by comparison of thin layer chromatography (TLC) behavior and the proton nuclear magnetic resonance (^{1}H-NMR), carbon-13 nuclear magnetic resonance (^{13}C-NMR) and infrared (IR) spectral data with those of an authentic sample. Furthermore, hydrolysis of **2** with β-glucosidase gave an aglycone (**2b**), colorless oil, which was identified as (+)-pinoresinol[1,5] by comparison of the ^{1}H-NMR, IR, MS and $[\alpha]_D$ data with those of an authentic sample.

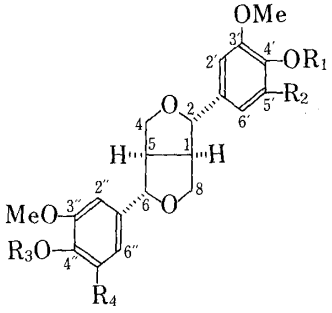
Glycoside **3** was isolated as colorless needles, $C_{34}H_{46}O_{18}$, mp 258 °C, $[\alpha]_D^{22}$ 0° (pyridine), whose molecular weight was observed at *m/z* 765 (M^++Na) on FD-MS. Glycoside **3** was identified as liriodendrin[3] by comparison of the ^{1}H-, ^{13}C-NMR and IR spectral data with those of an authentic sample. Furthermore, hydrolysis of glycoside **3** with β-glucocidase gave an aglycone (**3b**), colorless needles, which was identified as (+)-syringaresinol[5] by comparison of the ^{1}H-NMR, IR, MS and $[\alpha]_D$ spectral data with those of an authentic sample.

Glycoside **4** was isolated as amorphous, $C_{26}H_{32}O_{11}$, $[\alpha]_D^{22}$ +8.0° (MeOH), whose molecular weight was observed at *m/z* 544 (M^++1+Na) and 560 (M^++1+K) on FD-MS. Glycoside **4** was identified as (+)-pinoresinol *O*-β-D-glucopyranoside[1] by comparison of TLC and IR spectral data with those of an authentic sample. Furthermore, the acatate of **4** was studied. Acetylation of **4** with acetic anhydride-pyridine gave a pentaacetate (**4a**) as colorless needles, which was identified as (+)-pinoresinol *O*-β-D-glucopyranoside pentaacetate[1] by comparison of IR spectral data with those of an authentic sample.

Glycoside **1** moved intermediately between **2** and **3** on TLC. Glycoside **1** was isolated as colorless needles, $C_{33}H_{44}O_{17}$, mp 222 °C, $[\alpha]_D^{22}$ −9.1° (pyridine), whose molecular weight was

observed at m/z 734 ($M^+ - 1 + Na$) and 750 ($M^+ - 1 + K$) on FD-MS. The ultraviolet (UV) spectrum of **1**, which showed absorption maxima at 225 and 275 nm, was similar to those of **2**, **3** and **4**. The IR spectrum of **1** suggested the presence of aromatic ring (1595 and 1510 cm^{-1}). The ^1H-NMR spectrum of **1** showed signals at δ 7.60—6.98 (3H, m) and 6.60 (2H, s), due to aromatic protons and at 3.78 (9H, s), due to aromatic methoxy groups.

Acetylation of **1** with acetic anhydride-pyridine gave an octaacetate (**1a**) as colorless



1 : $R_1 = R_3 = Glc$, $R_2 = H$, $R_4 = OMe$
1a : $R_1 = R_3 = Glc(Ac)_4$, $R_2 = H$, $R_4 = OMe$
1b : $R_1 = R_2 = R_3 = H$, $R_4 = OMe$
2 : $R_1 = R_3 = Glc$, $R_2 = = R_4 = H$
2a : $R_1 = R_3 = Glc(Ac)_4$, $R_2 = R_4 = H$
2b : $R_1 = R_2 = R_3 = R_4 = H$
3 : $R_1 = R_3 = Glc$, $R_2 = R_4 = OMe$
3a : $R_1 = R_3 = Glc(Ac)_4$, $R_2 = R_4 = OMe$
3b : $R_1 = R_3 = H$, $R_2 = R_4 = OMe$
4 : $R_1 = R_2 = R_4 = H$, $R_3 = Glc$

Chart 1

TABLE I. ^{13}C-NMR Chemical Shifts (in DMSO-d_6)

Carbon	1	2	3	4	1a	2a	3a	2b	3b
C-1	53.6	53.7	53.6	53.7	53.7	53.8	53.7	53.7	53.8
5				53.5					
4, 8	71.2	71.1	71.4	71.0	71.2	71.1	71.3	71.0	71.1
2	85.0	84.8	85.0	85.1	84.9	84.7	84.9	85.2	85.3
6	84.8			84.9	84.7				
C-1′	135.2	135.3	134.0	132.3	137.5	137.5	133.2	132.4	131.5
1″	133.9			135.4	133.2				
2′	110.7	110.7	104.4	110.6	111.0	111.0	103.5	110.6	103.9
2″	104.3			110.8	103.5				
3′	145.9	145.9	152.6	146.0	145.1	145.0	152.6	146.0	147.9
3″	152.6				152.6				
4′	149.0	149.0	137.1	147.5	149.9	149.9	138.4	147.6	135.0
4″	137.1			149.1	138.4				
5′	115.5	115.6	152.6	115.2	118.1	118.1	152.6	115.2	147.9
5″	152.6			115.6	152.6				
6′	118.2	118.2	104.4	118.6	118.2	118.2	103.5	118.6	103.9
6″	104.3			118.2	103.5				
OCH_3	55.8	55.8	56.5	55.7	56.0	56.0	56.2	55.8	56.1
	56.4			55.9	56.2				
glc-1′	100.4	100.4	102.8	100.4					
1″	102.9								
2′	73.2	73.2	74.2	73.3	$OCOCH_3$				
2″	74.2				169.7 169.4 169.1 168.8	169.8 169.4 169.2 168.8	169.7 169.4 169.1 168.8		
3′	77.0	76.9	76.5	76.8					
3″	76.5								
4′	69.7	69.7	70.0	70.0	$OCOCH_3$				
4″	70.0				20.3	20.3	20.3		
5′	76.8	76.8	77.1	77.0					
5″	77.0								
6′	60.8	60.8	61.0	60.7					
6″	60.9								

needles, $C_{49}H_{60}O_{25}$, mp 168 °C, whose molecular weight was observed at *m/z* 1071 ($M^+ + Na$) on FD-MS. The ^{1}H-NMR spectrum of **1a** showed the presence of eight alcoholic acetyl groups at δ 2.20 and 1.98 (24H, each s), and aromatic protons at δ 7.12—6.76 (3H, m) and at 6.66 (2H, s).

Hydrolysis of **1** with β-glucosidase gave an aglycone (**1b**) as a white powder, $[\alpha]_D^{22}$ +37° ($CHCl_3$), whose ^{1}H-NMR, IR and MS spectral data were identical with those of (+)-medioresinol.[5] The presence of glucose in the hydrolysate was detected on TLC and gas chromatography (GC).

Thus, glycoside **1** was concluded to be (+)-medioresinol diglucoside. The position of the glucose linkage was determined as follows. The chemical shifts of C-1′ and C-1″ atoms of lignans are sensitive both to change in substituents on the aromatic ring and to their stereochemistry.[6] As to the chemical shifts of epipinoresinol *O*-β-D-glucopyranoside, Chiba *et al.*[6] reported a value of 135.4 ppm for C-1 atoms of equatorial guaiacyl groups linked to C-4-*O*-β-D-glucosyl groups. For glycoside **2**, the chemical shift of C-1′ is 135.3 ppm, which is essentially identical with the above value. The chemical shift of C-1″ of glycoside **3**, which has a syringyl group linked to the C-4″-*O*-β-D-glucosyl group, is 134.0 ppm. The shifts of the C-1′ and C-1″ atoms of glycoside **1** are 135.2 and 133.9 ppm, respectively. Comparison of the chemical shifts of **1**, **2** and **3** confirmed that **1** is (+)-medioresinol di-*O*-β-D-glucopyranoside. This is the first reported isolation of **1** as a natural product.

Sih *et al.*[2] reported the hypotensive activity of **2**, and Tempesta *et al.*[3] reported activity of **3** in the P-388 lymphocytic leukemia (PS) test system. Pharmacological studies of **1** and further investigation of the constituents of *Eucommia ulmoides* OLIV. are in progress.

Experimental

All melting points are uncorrected. The following instruments were used; melting point, Mettler FP-61; optical rotation value, JASCO DIP-4; UV spectra, Hitachi 200-20; IR spectra, Hitachi EPI-G2; GC, Hitachi 063 with a hydrogen flame ionization detector; EI-MS, Hitachi RMU-7L; FD-MS, JEOL-01-SG2; ^{1}H- and ^{13}C-NMR spectra, JEOL-FX-90-Q with tetramethylsilane (δ=0) as an internal reference.

Silica gel 60 F_{254} (Merck) and Cellulose F (Merck) precoated TLC plates were used for TLC. The spots were detected by spraying the plates with anisaldehyde–H_2SO_4 solution (anisaldehyde 2 ml, H_2SO_4 1 ml, EtOH 23 ml) for lignans, and diphenylamine–aniline–H_3PO_4 solution (diphenylamine 2 g, aniline 2 ml, acetone 100 ml, 80%H_3PO_4 10 ml) for glucose.

The abbreviations used for NMR data are as follows: s, singlet; d, doublet; t, triplet.

Isolation——The air-dried bark of *Eucommia ulmoides* OLIV. (5 kg) was chopped and extracted twice with hot MeOH. The MeOH solution was evaporated to a small volume under reduced pressure, then diluted with water and filtered. The filtrate was extracted with $CHCl_3$–MeOH–water (1 : 1 : 1). The upper phase was concentrated and the residue was extracted with EtOAc. The aqueous solution was applied to a charcoal column (for chromatography, Wako) and eluted successively with water (20 l), water–EtOH (95 : 5, 15 l), water–EtOH (4 : 1, 3 l), water–EtOH (1 : 1, 3 l), EtOH (3 l) and $CHCl_3$–MeOH–water (1 : 2 : 1, 4 l). The final eluate was concentrated and the residue was subjected to column chromatography, eluting with $CHCl_3$–MeOH (9 : 1, 4 : 1, 2 : 1). The fractions were monitored by TLC using $CHCl_3$–MeOH–water (70 : 30 : 5) as a developer. The fractions showing a TLC spot at *Rf* 0.30 (**2**), 0.37 (**1**), 0.41 (**3**) and 0.71 (**4**) were collected respectively and purified by silica gel chromatography and gel filtration on TSK-GEL HW-40 (Toyo Soda) with MeOH, yielding **1** (0.25 g), **2** (0.50 g), **3** (0.30 g) and **4** (0.24 g).

(+)-Medioresinol Di-*O*-β-D-glucopyranoside (1)——Colorless needles (from EtOH), mp 222 °C, $[\alpha]_D^{22}$ −9.1° (*c*= 0.1, pyridine). UV λ_{max}^{MeOH} nm: 225, 275. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1595, 1510 (aromatic ring). FD-MS *m/z*: 750 ($M^+ - 1 + K$, 30%), 734 ($M^+ - 1 + Na$, 100%). ^{1}H-NMR (in DMSO-d_6) δ: 7.60—6.98 (3H, m, arom. H on guaiacyl ring), 6.60 (2H, s, arom. H on syringyl ring), 3.78 (9H, s, 3×OCH_3).

(+)-Medioresinol Di-*O*-β-D-glucopyranoside Octaacetate (1a)——**1** was acetylated with acetic anhydride-pyridine in the usual way. The crude acetate was purified by silica gel chromatography with $CHCl_3$–MeOH (20 : 1), and recrystallized from EtOH as colorless needles, mp 168 °C. IR ν_{max}^{KBr} cm^{-1}: 1750 (C=O), 1600, 1510 (aromatic ring). FD-MS *m/z*: 1071 ($M^+ + Na$, 75%), 718 ($M^+ - 331 + 1$, 60%), 331 (95%), 289 ($331 - CH_2O$, 100%). ^{1}H-NMR (in DMSO-d_6) δ: 7.12—6.76 (3H, m, arom. H on guaiacyl ring), 6.66 (2H, s, arom. H on syringyl ring), 3.76 (9H, s, 3×OCH_3), 2.02, 1.98 (24H, each s, 8×$OCOCH_3$).

Enzymatic Hydrolysis of 1——**1** (200 mg) was hydrolyzed with β-glucosidase (100 mg, Miles Laboratories) in

acetate buffer (0.1 N HOAc : 0.1 M NaOAc = 1 : 2, pH 5.0) for 2 d at 37 °C. The reaction mixture was extracted with Et_2O (50 ml × 2) and the residue obtained from the organic phase was chromatographed on silica gel. Elution with $CHCl_3$–MeOH (20 : 1) gave a pure aglycone (**1b**, 20 mg). The aqueous layer was evaporated to dryness, and the residue was spotted on a precoated TLC plate (Cellulose F, Merck) and developed with EtOAc : pyridine : HOAc : water = 5 : 5 : 1 : 3. The plate was sprayed with diphenylamine–aniline–H_3PO_4 solution (diphenylamine 2 g, aniline 2 ml, acetone 100 ml and 80% H_3Po_4 10 ml) and heated at 80 °C. The yellow spot at *Rf* 0.33 was identified as glucose by comparison with an authentic sample.

(+)-Medioresinol (1b)——White powder (from EtOH), $[\alpha]_D^{22}$ +37° (*c* = 0.1, $CHCl_3$) [lit.[5] $[\alpha]_D$ +57° ($CHCl_3$)]. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1610, 1515 (aromatic ring). EI-MS *m/z*: 388 (M^+, 100%), 357 ($M^+ - OCH_3$, 8%), 167 (25%), 151 (45%), 137 (28%). ^{1}H-NMR (in $CDCl_3$) δ: 6.96—6.80 (3H, m, arom. H on guaiacyl ring), 6.58 (2H, s, arom. H on syringyl ring), 4.80—4.64 (2H, m, $H_{2,6}$), 4.40—3.80 (4H, m, $H_{4,8}$), 3.20—3.00 (2H, m, $H_{1,5}$). ^{1}H-NMR, MS and IR data of **1b** were identical with those of (+)-medioresinol.

(+)-Pinoresinol Di-*O*-β-D-glucopyranoside (2)——White powder (from EtOH), $[\alpha]_D^{22}$ −24.1° (*c* = 0.1, MeOH) [lit.[2] $[\alpha]_d^{25}$ −27.3° (H_2O)]. UV λ_{max}^{MeOH} nm: 227, 278. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1600, 1510 (aromatic ring). FD-MS *m/z*: 721 (M^+ + K, 25%), 705 (M^+ + Na, 100%). ^{1}H-NMR (in DMSO-d_6) δ: 7.12—6.78 (6H, m, arom. H on guaiacyl ring), 3.78 (6H, s, 2 × OCH_3). The TLC, ^{1}H-, ^{13}C-NMR, $[\alpha]_D$ and IR data of **2** were identical with those of (+)-pinoresinol di-*O*-β-D-glucopyranoside.

Enzymatic Hydrolysis of 2——**2** (200 mg) was hydrolyzed in the same way as described for **1** to give a pure aglycone (**2b**, 20 mg) and glucose. Glucose was detected in the same way as described above.

(+)-Pinoresinol (2b)——Colorless oil, $[\alpha]_D^{20}$ +51° (*c* = 0.1, $CHCl_3$) [lit.[1] $[\alpha]_D^{21}$ +61.6° ($CHCl_3$)]. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1610, 1510 (aromatic ring). EI-MS *m/z*: 358 (M^+, 100%), 163 (26%), 151 (80%), 137 (27%), 69 (59%). ^{1}H-NMR (in $CDCl_3$) δ: 6.92—6.80 (6H, m, arom. H on guaiacyl ring), 4.73 (2H, d, *J* = 5 Hz, $H_{2,6}$), 4.36—3.64 (4H, m, $H_{4,8}$), 3.87 (6H, s, 2 × OCH_3), 3.2—3.0 (2H, m, $H_{1,5}$). The ^{1}H-NMR, MS and IR data were identical with those of (+)-pinoresinol.

Liriodendrin (3)——Colorless needles (from water), mp 258 °C, $[\alpha]_D^{22}$ 0° (*c* = 0.1, pyridine) [lit.[3] mp 265—266 °C, $[\alpha]_D^{25}$ −12.1° (pyridine)]. UV $\lambda_{max}^{H_2O}$ nm: 227, 272. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1595, 1505 (aromatic ring). FD-MS *m/z* add. NaI: 765 (M^+ + Na, 23%), 394 (100%); add. none: 418 ($M^+ - 2 \times C_6H_{11}O_5 + 2$, 100%). ^{1}H-NMR (in DMSO-d_6) δ: 6.64 (4H, s, arom. H on syringyl ring), 3.78 (12H, s, 4 × OCH_3). *Anal.* Calcd for $C_{34}H_{46}O_{18}$: C, 54.98; H, 6.24. Found: C, 54.76; H, 6.25.

Liriodendrin Octaacetate (3a)——**3** was acetylated in the same way as described for **1a** to give octaacetate (**3a**), colorless needles (from EtOH), mp 119.3 °C (lit.[3] mp 121—124 °C). IR ν_{max}^{KBr} cm^{-1}: 1750 (C=O), 1600, 1505 (aromatic ring). FD-MS *m/z* add, NaI: 1101 (M^+ + Na, 100%); add. none: 1078 (M^+, 15%), 747 ($M^+ - 331$, 70%), 331 (100%). ^{1}H-NMR (in DMSO-d_6) δ: 6.66 (4H, s, arom. H on syringyl ring), 3.76 (12H, s, 4 × OCH_3), 2.00 (24H, s, 8 × $OCOCH_3$).

Enzymatic Hydrolysis of 3——**3** was hydrolyzed in the same way as described for **1** to give an aglycone (**3b**) and glucose. Glucose was detected as described above.

(+)-Syringaresinol (3b)——Colorless needles, mp 183.5 °C, $[\alpha]_D^{20}$ +44.0° (*c* = 0.1, $CHCl_3$) [lit.[5] mp 171—173 °C, $[\alpha]_D$ +19.0° ($CHCl_3$)]. High-resolution EI-MS *m/z*: 418.1620 [M^+($C_{21}H_{26}O_8$), 100%], 388.1325 ($M^+ - OCH_2$, 30%). ^{1}H-NMR (in $CDCl_3$) δ: 6.60 (4H, s, arom. H on syringyl ring), 4.61 (2H, d, *J* = 4 Hz, $H_{2,6}$), 4.27—3.64 (4H, m, $H_{4,8}$), 3.87 (12H, s, 4 × OCH_3), 3.18—2.92 (2H, m, $H_{1,5}$). The ^{1}H-NMR, MS and IR data of **3b** were identical with those of (+)-syringaresinol.

(+)-Pinoresinol *O*-β-D-Glucopyranoside (4)——Amorphous, $[\alpha]_D^{22}$ +8.0° (*c* = 0.1, MeOH) [lit.[1] $[\alpha]_D^{20}$ +8.6° (EtOH)]. UV λ_{max}^{MeOH} nm: 227, 278. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1600, 1510 (aromatic ring). FD-MS *m/z*: 1064 ($2M^+$ + 1 + Na, 55%), 560 (M^+ + 1 + K, 15%), 544 (M^+ + 1 + Na, 100%). *Rf*: 0.35 (Silica gel 60F_{254}, $CHCl_3$: EtOH = 4 : 1). TLC behavior and IR spectral data were identical with those of (+)-pinoresinol *O*-β-D-glucopyranoside.

(+)-Pinoresinol *O*-β-D-Glucoside Pentaacetate (4a)——Amorphous, IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O), 1610, 1510 (aromatic ring). *Rf*: 0.52 (Silica gel 60F_{254}, $CHCl_3$: EtOAc = 1 : 1). TLC behavior and IR spectral data of **4a** were identical with those of (+)-pinoresinol *O*-β-D-glucoside pentaacetate.

Detection of Glucose by GC from Glycosides 1, 2 and 3——Glucose in **1**, **2** and **3** was also detected as glucitol acetate by GC. **1** (10 mg) was hydrolyzed with 10% H_2SO_4 (1 ml) for 1 h and then cooled. The reaction mixture was extracted with Et_2O and the aqueous layer was passed through an Amberlite IRA-45 column, which was washed with water. The eluate was concentrated under reduced pressure, then treated with $NaBH_4$ (5 mg) and stirred for 1 h at room temperature. The reaction mixture was passed through an IR-120 (H^+) column, which was washed with water. The eluate was concentrated to dryness. H_3BO_3 was removed by codistillation with MeOH. The residue was acetylated with acetic anhydride (1 ml) and pyridine (1 ml) at 100 °C for 1 h. The reaction mixture was diluted with water and then concentrated. The presence of 1,3,5,6-tetra-*O*-acetyl-2,4,-di-*O*-methyl-glucitol [t_R (min) 16.3] in this residue was detected by GC. Conditions: column, 1.5% OV-17 3 mm × 1 m; column temperature, 200 °C; carrier gas, N_2, 30 ml/min; injection temperature, 280 °C.

2 and **3** were treated in a similar way and glucitol acetate was detected.

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