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ORIGINAL ARTICLE

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Two lignan rhamnosides from birch leaves

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Abstract The extractives of shirakamba (*Betula platyphylla* Sukatchev var. *japonica* Hara) leaves were investigated. Two lignan glycosides were isolated, and their structures were elucidated to be 1-(4′-hydroxy-3′-methoxyphenyl)-2-[1″-(3-α-L-rhamnopyranosyloxypropyl)-3″-hydroxyphenoxy]-1,3-propanediol (I) and a new 2,3-dihydro-2-arylbenzofuran configuration neolignan, *cis*-2,3-dihydro-2-(4′-α-L-rhamnopyranosyloxy-3′-methoxyphenyl)-3-hydroxymethyl-7-hydroxy-5-benzofuranpropanol (II). These neolignan rhamnosides were newly found in shirakamba.

Key words Lignan · Rhamnoside · Birch · *Betula platyphylla* Sukatchev var. *japonica* Hara

Introduction

Shirakamba (*Betula platyphylla* Sukatchev var. *japonica* Hara; Betulaceae) is a tall deciduous tree that grows on Hokkaido and Honshu islands in Japan. It has not been widely used in Japan except as pulp chip and for chopsticks production from its wood.

Some studies on the extractives of living tissue of shirakamba have been published to date. The inner bark of the shirakamba contains a large amount of phenolic glycosides, including platyphylloside,[1] which has an inhibitory effect on ruminant digestibility in vitro.[2] Little is known about the extractives of birch leaves, although it was reported that 3,4′-dihydroxypropiophenone-3-β-D-glucopyrannoside, four terpernoids, and two flavonol glycosides have been found.[3,4] Traditionally, extractives from the leaves were expected to be a source of compounds that increase the activity of the antioxidative defense of human blood plasma.[5] The birch flowers and leaves have been utilized as a herbal tea in Bulgaria.

In this work we studied the extractives from the leaves of shirakamba to obtain basic information on their chemical components to utilize the leaves as a resource for medicinal reagents in the future.

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Results and discussion

Ethanol extracts from the leaves of shirakamba (*Betula platyphylla* Sukatchev var. *japonica* Hara) were investigated by several chromatographic techniques. Two compounds, I and II (Fig. 1), were isolated after extraction with EtOAc saturated with water.

Compound I was obtained as an acetyl derivative IA because purifying it from its natural state was difficult using the methods in this work. The acetate IA showed a parent ion (M^+) at m/z 804 in the field desorption mass spectrum (FD-MS). In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of acetate IA (Table 1), ABX spin systems at δ 6.86–7.05 (6H) were assignable to six correlated aromatic protons, indicating the existence of two 1,3,4-trisubstituted aromatic rings. In the two-dimensional homonuclear chemical shift-correlated spectroscope (^{1}H-^{1}HCOSY) of acetate IA, methylene protons of C_β [δ 1.89 (2H, m) correlated with benzyl protons at C_α [δ 2.65 (2H, t, J = 6.0Hz)] and methylene protons at C_γ [δ 3.42 (1H, m), 3.70 (1H, m)], which correspond to three methylene protons of the side chain of the pendant group ring A. On the other hand, methylene protons at C_3 [2H, δ 4.04 (dd, J = 5.7, 12.1Hz, threo), 4.19 (dd, J = 4.2, 12.1Hz, threo), 4.10 (dd, J = 4.8, 11.8Hz, erythro), and 4.37 (dd, J = 5.8, 11.9Hz, erythro)] and a methine proton at C_2 [δ 4.68 (1H, m)] were observed; and a methine proton at C_1 [1H, δ 6.03 (d, J = 4.3Hz, erythro), 6.07 (d, J = 7.1Hz, threo)] correlated with the methine proton at C_2, explicable by the glycerol side chain of an aromatic ring (ring B). In the heteronuclear multiple bond correlation (HMBC) spectrum, the methine proton at C_2 (δ 4.68) correlated with the signal of C-4″ of the

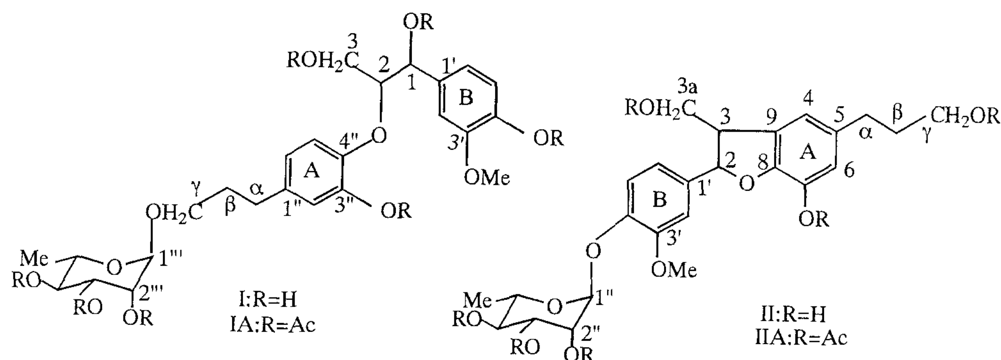

Fig. 1. Structures of the lignan rhamnosides isolated from the leaves of *Betula platyphylla* Sukatchev var. *japonica* Hara

Table 1. ^{1}H-NMR spectral data of the acetates IA and IIA[a]

Protons	IA	IIA
Aglycone moieties		
Aromatic ring		
H-2″ (H-6)*	6.86 (1H, d, J = 1.6 Hz)	6.80 (1H, d, J = 1.5 Hz)
H-5″ (H-4)*	6.89 (1H, d, J = 8.8 Hz)	6.88 (1H, brs)
H-6″, 6′	6.96-7.00 (2H, m)	
H-2′	7.01 (1H, d, J = 2.6 Hz)	6.97 (1H, d, J = 1.7 Hz)
H-5′	7.05 (1H, d, J = 8.4 Hz)	7.05 (1H, d, J = 8.1 Hz)
(H-6′)*		6.85 (1H, dd, J = 1.7, 8.1 Hz)
3′-OMe	3.83 (3H, s)	3.84 (3H, s)
Phenolic-OAc	2.30 (3H, s), 2.27 (3H, s)	2.30 (3H, s)
H-1 (H-2)*	1H, 6.03 (d, J = 4.3 Hz, *erythro*)	5.52 (1H, d, J = 2.0 Hz)
	6.07 (d, J = 7.1 Hz, *threo*)	–
H-2 (H-3)*	4.68 (1H, m)	3.70 (1H, m)
H-3 (H-3a)*	2H, 4.04 (dd, J = 5.7, 12.1 Hz, *threo*)	4.29 (1H, dd, J = 8.1, 11.1 Hz)
	4.19 (dd, J = 4.2, 12.1 Hz, *threo*)	4.44 (1H, dd, J = 5.4, 11.1 Hz)
	4.10 (dd, J = 4.8, 11.8 Hz, *erythro*)	–
	4.37 (dd, J = 5.8, 11.9 Hz, *erythro*)	–
H-α	2.65 (2H, t, J = 6.0 Hz)	2.63 (2H, t, J = 7.4 Hz)
H-β	1.89 (2H, m)	1.92 (2H, m)
H-γ	3.42 (1H, m), 3.70 (1H, m)	4.09 (2H, t, J = 6.6 Hz)
Sugar moiety		
H-1‴ (H-1″)*	4.71 (1H, d, J = 1.5 Hz)	5.36 (1H, d, J = 1.7 Hz)
H-2‴ (H-2″)*	5.25 (1H, m)	5.51 (1H, d, J = 3.5 Hz)
H-3‴ (H-3″)*	5.32 (1H, m)	5.55 (1H, dd, J = 3.5, 10.1 Hz)
H-4‴ (H-4″)*	5.07 (1H, t, J = 9.9 Hz)	5.14 (1H, t, J = 10.1 Hz)
H-5‴ (H-5″)*	3.87 (1H, m)	4.15 (1H, m)
H-6‴ (H-6″)*	1.21 (3H, d, J = 6.2 Hz)	1.20 (3H, d, J = 6.4 Hz)
Alcoholic-OAc	1.96–2.18 (15H, m)	2.02–2.17 (15H, m)

s, singlet; d, doublet; dd, double doublet; m, multiplet; J, coupling constant; *, acetate IIA; brs, broad singlet

[a] At 500 Hz, in $CDCl_3$, TMS as internal standard

aromatic ring A, the position of the ether linkage between the arylglycerol moiety (ring B), and the arylpropanol moiety (ring A). These data suggested that the acetate IA was a β-O-4-aryl ether type lignan. The doublet at δ 6.03 was assigned to the methine proton at C_1 of the arylglycerol moiety (ring B) of an erythro isomer, and the other doublet at δ 6.07 was assigned to that of a threo isomer.[6] The ratio of the erythro and threo isomers was calculated to be 1.0:1.5 by the relative intensities of the two doublets of the methine proton at C_1 in the ^{1}H-NMR spectrum. A singlet a δ 3.83 (3H) was assigned to methyl protons of a phenolic methoxyl group. Multiplets at δ 1.96–2.18 (15H, m) and two singlets at δ 2.27 (3H) and 2.30 (3H) were derived from the methyl protons of the acetyl groups of five alcoholic and two phenolic groups. The electron impact mass spectrum (EI-MS) of the acetate IA showed a characteristic ion at m/z 179, which was attributed to the $^+CH_2$-Ar(OAc)(OMe).

By comparing the ^{13}C-NMR spectral data of the acetate IA with those of the previously reported rhamnoside,[7–10] which showed six resonances at δ 97.4 (C-1‴), 70.0 (C-2‴), 69.1 (C-3‴), 71.2 (C-4‴), 66.3 (C-5‴), and δ 17.4 (C-6‴) (Table 2), the existence of a rhamnosyl residue in the acetate IA was clarified. The mode of the rhamnosidic linkage was determined to be an α-from based on the small coupling constant of the doublet at δ 4.71 (1H, d, J = 1.5 Hz) of the anomeric proton signal. The long-range connectivities ob-

Table 2. ^{13}C-NMR spectral data of the acetates IA and IIA[a]

C	IA	IIA
Aglycone moieties		
C-1 (C-2)*	73.4, 74.2	88.6
C-2 (C-3)*	78.5, 79.1	51.5
C-3 (C-3a)*	62.1, 62.3	65.9
C-α	31.3	31.9
C-β	30.8	30.7
C-γ	67.1	64.1
C-1′	134.7, 134.8	137.3
C-2′	111.7, 115.6	110.3
C-3′	151.1, 151.2	151.5
C-4′	139.8, 140.1	145.3
C-5′	122.7, 122.9	119.4
C-6′	119.4, 119.7	118.2
C-1″ (C-5)*	135.6, 136.1	128.6
C-2″ (C-6)*	123.2, 123.3	122.4
C-3″ (C-7)*	140.6, 141.1	135.2
C-4″ (C-8)*	147.3, 147.8	149.5
C-5″ (C-9)*	116.6	134.3
C-6″ (C-4)*	126.5, 126.6	122.8
3′-OMe	56.0	56.4
Sugar moieties		
C-1‴ (C-1″)*	97.4	97.9
C-2‴ (C-2″)*	70.0	69.4
C-3‴ (C-3″)*	69.1	70.2
C-4‴ (C-4″)*	71.2	71.5
C-5‴ (C-5″)*	66.3	67.8
C-6‴ (C-6″)*	17.4	17.8

* Acetate IIA
[a] At 125 MHz, in $CDCl_3$, TMS as internal standard

served in the HMBC spectrum of the acetate IA indicates that the anomeric proton signal at δ 4.71 correlates with the signal of C-γ. Thus, compound I is identified to be 1-(4′-hydroxy-3′-methoxyphenyl)-2-[1″-(3-α-L-rhamnopyranosyloxypropyl)-3″-hydroxyphenoxy]-1,3-propanediol, which was obtained from the needles of *Pinus massoniana* Lamb (Pinaceae).[11]

Compound II was positive in diazotized sulfanilic acid (DSA), indicating that compound II is a phenolic compound. The M^+ of compound II was m/z 492, and its acetyl derivative IIA gave an M^+ m/z 744. The difference of the two molecular ions indicate that compound II has six free hydroxyl groups ($42 \times 6 = 252$). An ^{1}H-NMR spectrum of the acetate IIA (Table 1) showed the characteristic signals of aromatic protons of a dihydrobenzofuran type lignan structure, namely, two doublets at δ 6.80 (1H, d, J = 1.5 Hz) and δ 6.88 (1H, brs) which were assigned to aromatic protons at C_6 and C_4 (ring A). A doublet at δ 5.52 (1H, d, J = 2.0 Hz) and a multiplet δ 3.70 (1H, m) were assigned to two methine protons of C_2, C_3 of the dihydrobenzofuran structure, respectively. The relative configuration of C-2 and C-3 was deduced from a comparison of the ^{1}H-NMR spectrum of the acetate IIA with that of the known 2,3-dihydro-2-aryl-benzofuran neolignans. Thus, it was known that the coupling constant $J_{2,3}$ was larger for the trans than for the cis isomer. Because the acetylated neolignan had a coupling constant of $J_{2,3,}$ = 6.0 Hz, it was assigned at the trans isomer.[12] In this case the acetate IIA had a coupling constant of $J_{2,3}$ = 2.0 Hz, indicating that it is a cis isomer. Two double doublets at δ 4.29 (1H, dd, J = 8.1, 11.1 Hz) and δ 4.44 (1H, dd, J = 5.4, 11.1 Hz) originated from the methylene proton at C_{3a}. Two doublets at δ 7.05 (1H, d, J = 8.1 Hz) and δ 6.97 (1H, d, J = 1.7 Hz) and a double doublet a δ 6.85 (1H, dd, J = 1.7, 8.1 Hz) were assigned to three aromatic protons at $C_{5'}$, $C_{2'}$, and $C_{6'}$ of an ABX spin system (ring B), respectively. In the ^{1}H-^{1}HCOSY of the acetate IIA, methylene protons at C_β [δ 1.92 (2H, m)] were correlated with benzyl protons at C_α [δ 2.63 (2H, t, J = 7.4 Hz)] and methylene protons at C_γ [δ 4.09 (2H, t, J = 6.6 Hz)]. They correspond to three methylene protons of the side chain of the pendant group ring A. Furthermore, a singlet at δ 3.84 (3H) was assigned to a phenolic methoxyl group, and irradiation on the methoxyl group of the acetate IIA caused strong enhancement of the peak of the aromatic proton at $C_{2'}$ only. Thus, the methoxyl group was close to $C_{2'}$, indicating that the acetate IIA has the methoxyl group at $C_{3'}$. A singlet at δ 2.30 was assigned to methyl protons of a phenolic acetoxyl group. Five singlets at δ 2.02, 2,04, 2.05, 2.07, and 2.17 were assigned to those of the alcoholic acetoxyl groups of the sugar moiety.

On the other hand, the presence of the rhamnosyl residue in the acetate IIA was suggested by a ^{13}C-NMR spectrum (Table 2). The spectrum showed six resonances at δ 97.9 (C-1″), 69.4 (C-2″), 70.2 (C-3″), 71.5 (C-4″), 67.8 (C-5″), and 17.8 (C-6″) being considered with those of rhamnosyl residue.[7–10] The mode of the rhamnosidic linkage was determinded to be an α-form based on the coupling constant of the doublets at δ 5.36 (1H, d, J = 1.7 Hz) of the anomeric proton signal. The anomeric proton at $C_{1'''}$ of the acetate IIA in the ^{1}H-NMR spectrum, compared with the data of the anomeric proton at $C_{1'''}$ of the acetate IA, showed an obvious downfield shift signal at δ 5.36, which indicated that the rhamnosyl residue is located on the aromatic ring. Placement of the rhamnosyl residue on the aglycone was verified by use of the proton nuclear overhauser effect difference spectrum (^{1}H-NOEDS) of the acetate IIA. Irradiation on the anomeric proton of the rhamnoseyl moiety of the acetate IIA caused strong enhancement of the peak of an aromatic proton at $C_{5'}$ [δ 7.05 (1H, d, J = 8.1 Hz)]. This result proves that the rhamnosyl residue is linked to C-4′. Thus, it is concluded that compound II is *cis*-2,3-dihydro-2-(4′-α-L-rhamnopyranosyloxy-3′-methoxyphenyl)-3-hydroxymethyl-7-hydroxy-5-benzofuranpropanol, which was obtained from the needles of *Pinus massoniana* Lamb[11] and the root bark of *Picea abies* (L) Karst (Pinaceae).[13] Li et al.[12] claimed that there was no evidence of the occurrence of 2,3-dihydrobenzofuran neolignans with a *cis* configuration in nature based on a ^{1}H-NMR data comparison of the synthetic neolignan and those of the naturally occurring neolignans.[14–18] However, our study clarified that it has a *cis* configuration, which indicates that compound II is the only case occurring in *cis* form.

Although the two lignan rhamnosides and their aglycones had been isolated from *Pinus massoniana* Lamb,[11] *Picea abies* (L) Karst,[13] and *Pinus sylvestris*,[19] no report on their isolation from the leaves of shirakamba (*Betula platyphylla* Sukatchev var. *japonica* Hara) has been found so far. Because a number of lignans were isolated as

Table 3. Neolignans reported so far

Type	Origin	Reference
β-O-4	Pinaceae	
	Pinus massoniana (needles)	11
	Pinus sylvestris (needles)	19
	Picea abies (root bark, needles)	13, 21
	Larix leptolepis (wood, inner bark)	22, 23
	Boraginaceae	
	Ehretia ovalifolia (bark)	24
Benzofuran	Pinaceae	
	Pinus sylvestris (needles)	19
	Pinus silvestris (needles)	25
	Picea abies (root bark)	21
	Alangiaceae	
	Alangium platanifolium var. *trilobum* (stem bark)	26
	Alangium premnifolium (stem)	27
	Betulaceae	
	Corylus sieboldiana (wood)	28
Bicyclooctane	Lauraceae	
	Aniba sp. (wood)	29
	Nectandra miranda (wood)	30
	Ocotea catharinensis (leaves)	31
Tetrahydrofuran	Lauraceae	
	Aniba sp. (wood)	29
α-α	Pinaceae	
	Pinus massoniana Lamb (needle)	11
5-5	Magnoliaceae	
	Magnolia obovata Thunberg (bark)	32
β-1	Pinaceae	
	Larix leptolepis (sapwood)	22

rhamnosides, the formation of lignan rhamnosides seems to be a common phenomenon in plants.

Earlier, lignans were designated mainly by the compounds constructed from two phenylpropane units with β-β linkage in their side chains. McCredie et al.[20] proposed in 1968 that the definition be extended to cover all low-molecular-weight natural products formed by the oxidative coupling of two *p*-hydroxyphenylpropane units. They were called "neolignans." Many neolignans have now been isolated with a wide scope in plants (Table 3). Structures of all the neolignans described above are similar to those of dimeric structural units of lignin. The compounds with β-O-4 and benzofuran structures were first obtained from the hydrolysis products of lignin.[33–35] Thus, the biogenesis of these neolignans seems to be similar to that for the dimeric structural units of lignin. However, most of the naturally occurring lignans and neolignans are produced in optically active forms, and the compounds isolated in this study showed optical activities, indicating that the formation of lignans and neolignans proceeds under strict enzymatic control, in contrast to the racemic formation of the dimeric structural units in lignin.

Experiment

^{1}H-NMR spectra were measured on a Bruker AM-500 (^{1}H: 500MHz; ^{13}C: 125MHz) using deuterated chloroform $(CDCl)_3$ as a solvent and tetramethylsilane (TMS) as an internal standard. Two-dimensional (2D)-NMR was performed by ^{1}H-^{1}H, ^{1}H-^{13}C COSY, and HMBC. FD-MS was obtained by a JEOLJWS-01SG-2 mass spectrometer. High-performance liquid chromatography (HPLC) was conducted on a JASCO 880-PU (pump) with JASCO 875-UV (detector) system. Thin-layer chromatography (TLC) was performed on a Wakogel B-10 and Kiesselgel 60 system using the solvents chloroform:methanol:water (H_2O) (CMW, 40:10:1, v/v), acetone:ethyl acetate (EtOAc):water (AEAW, 10:10:1, v/v), and hexane:ethyl acetate (HEA, 1:1, v/v).

Extraction and isolation

Shirakamba leaves (2.72kg) were collected in September 1995 at the Sapporo nursery garden of Hokkaido University. The leaves were extracted three times with 95% ethanol (EtOH) at room temperature for 24h. The EtOH solutions were combined and concentrated to a syrup (279.2g) under reduced pressures. Part of the syrup was then extracted successively with EtOAc, and the EtOAc was saturated with water and EtOH. The yields of each soluble fraction were 15.7, 8.1 and 25.4g, respectively.

The EtOAc saturated with the water-soluble fraction of the EtOH extraction was chromatographed on a silica gel (Wakogel C-200) column using EtOAc saturated with water. Each fraction was collected in 500-ml portions, moni-

tored by TLC with AEAW. The fractions containing the same compounds were combined, and F_1–F_6 were obtained.

Compound I was isolated from F_2. After acetylation of F_2, the main compound was separated by HPLC using a Wakosil-5C18HG column (20 × 250 mm) at 35°C. A developing solvent was a gradient of acetonitrile and H_2O (1:1–1:0, v/v) for 60 min. The flow rate was 5.0 ml/min monitered by an ultraviolet (UV) detector at 280 nm, and the acetate IA (5 mg) was isolated.

Compound II was isolated from F_4, separated by silica gel column chromatography using CMW (60:10:1) as a developing solvent in 30-ml portions. The fractions were monitored by TLC with CMW (40:10:1), and Fr_{4-1}–Fr_{4-8} were obtained. F_{4-8} was rechromatographed on a silica gel column using CMW (60:10:1, v/v) as the developing solvent in 10-ml portions. F_{4-8-1}–F_{4-8-3} were combined. F_{4-8-3} was rechromatographed on a silica gel column using CMW (60:10:1, v/v) to yield compound II (3 mg).

Acetylation of the compounds was conducted with acetic anhydride and pyridine at 55°C for 24 h.

Compound I

TLC (CMW, 40:10:1, v/v): Rf 0.28. IA: TLC (SG-III): Rf 0.40. FD-MS m/z: 804 (M^+). $[\alpha]_D^{25}$-17.4 (c = 0.12 in $CDCl_3$). UV λ_{max}^{EtOH} nm (log ε): 275 (3.72). IR υ_{max}^{KBr} cm^{-1} (%): 2926 (73.9), 1751 (100), 1509 (69.5), 1373 (60.9), 1226 (53.9), 1048 (47.8), and 758 (47.8). EI-MS m/z: 762 (M^+-42), 702 (M^+-42–60), 642 (M^+-42–60 × 2), 600 (M^+-2 × 42–60 × 2), 482, 440, 323, 273 (rahmnosyl residue in the form of acetate), 222, 179, 153, and 111 (derived from the rahmnosyl residue), 43. ^{1}H-NMR ($CDCl_3$): see Table 1. ^{13}C-NMR ($CDCl_3$): see Table 2. HPLC: Rt 20.8 min.

Compound II

TLC (CMW, 40:10:1, v/v): Rf 0.21. Acetylation of compound II gave a hexacetate IIA. IIA: TLC (HEA, 1:1, v/v): Rf 0.50. FD-MS m/z: 744 (M^+). $[\alpha]_D^{25}$ + 10.4 (c = 0.12 in $CDCl_3$). UV λ_{max}^{EtOH} nm (log ε): 280 (3.41). IR υ_{max}^{KBr} cm^{-1}(%): 1749 (100), 1457 (36), 1374 (39), 1222 (55), and 1039 (36). ^{1}H-NMR ($CDCl_3$): see Table 1. ^{13}C-NMR a ($CDCl_3$): see Table 2.

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