Phenolic Constituents of the Aerial Parts of *Cimicifuga simplex* and *Cimicifuga japonica*

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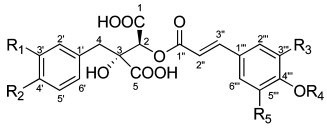
Chemical investigation of the aerial parts of *Cimicifuga simplex* afforded four new fukinolic acid analogues, cimicifugic acids K−N (**1**−**4**), and 10 known compounds, and *C. japonica* afforded three new fukinolic acid analogues, cimicifugic acids K−M (**1**−**3**), a new phenolic glycoside, shomaside F (**5**), and 10 known compounds. Cimicifugic acids K−N showed more potent hyaluronidase inhibitory activities than rosmarinic acid.

Cimicifuga simplex Wormsk. and *C. japonica* (Thunb.) Spreng. are Japanese plants in the genus *Cimicifuga* (Ranunculaceae). *C. simplex* is prescribed as one of the source plants of "Cimicifugae Rhizome" in the Japanese and Chinese Pharmacopoeias. "Cimicifugae rhizome" is used for anti-inflammatory, analgestic, and antipyretic treatment in traditional Chinese medicine.[1−3] As chemical constituents of the rhizomes of *Cimicifuga* species, triterpene glycosides, fukiic acid esters, piscidic acid esters, cinnamic acid derivatives, and chromones have been identified.[4−8] The extract of the rhizome of *C. racemosa* (L.) Hutt. has been reported to improve skin disorders.[9] The structures of fukiic acid derivatives are similar to that of rosmarinic acid, which has shown strong hyaluronidase inhibitory activity.[10] In the course of our studies on the water-soluble constituents of aerial parts of *C. simplex*, we obtained four new fukiic acid derivatives, cimicifugic acids K−N (**1**−**4**), and 10 known compounds (fukinolic acid,[11] cimicifugic acids A,[12] B,[12] D,[13] E,[13] and I,[8] caffeic acid, ferulic acid, isoferulic acid, 3,4-dimethoxycinnamic acid) and on that of aerial parts of *C. japonica* we obtained three new fukiic acid derivatives, cimicifugic acids K−M (**1**−**3**), and a new phenolic glycoside, shomaside F (**5**), along with 10 known compounds (fukinolic acid,[10] cimicifugic acids A−E,[12,13] G,[14] and I,[8] caffeic acid, ferulic acid). The present report deals with the isolation of these constituents, the structural elucidation of the new compounds, and their hyaluronidase inhibitory activities. As a result, it was found that compounds **1**−**4** showed a stronger inhibitory activitiy in the assay than rosmarinic acid.



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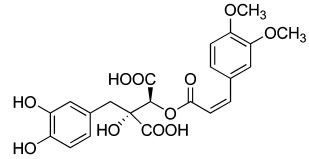
2	H	OH	OCH_3	CH_3	H
3	H	H	OH	H	H



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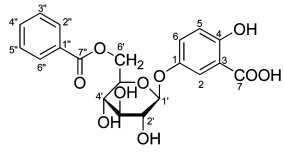

5

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Results and Discussion

The MeOH eluate obtained from a Mitsubishi Diaion HP-20 column was subjected to preparative HPLC, affording five new compounds (**1**−**5**) together with known compounds, which were identified by comparison of NMR data with reported data.

Cimicifugic acid K (**1**) was isolated as a pale brown powder. The molecular formula was established as $C_{20}H_{18}O_9$ on the basis of the HRFABMS data ($[M - H]^-$ ion at *m*/*z* 401.0907). The difference in the molecular formula of compound **1** when compared with that of cimicifugic acid C[12] was due to a lack of an oxygen atom. The UV absorption maximum (MeOH) at 316 nm (log ε 4.40) was indicative of an oxycinnamoyl residue.[8] The ^{1}H NMR spectrum of **1** indicated the presence of a piscidic acid moiety showing typical AB-type proton signals assignable to isolated methylene protons at δ 2.99 and 3.09 (each 1H, brd, J = 14 Hz), an oxymethine proton signal at δ 5.66 (1H, s, H-2), and a 1,4-disubstituted benzene moiety at δ 7.09 (2H, d, J = 7 Hz, H-2′, H-6′) and 6.66 (2H, d, J = 7 Hz, H-3′, H-5′). The ^{13}C NMR spectrum of **1** showed a methylene carbon signal (δ 42.0), an oxymethine carbon signal (δ 77.5), a quaternary carbon signal (δ 80.0), and two carboxyl carbon signals (δ 170.4 and 174.7), suggesting that **1** contains a piscidic acid moiety. In addition, a *p*-coumaroyl moiety was evident from ^{1}H NMR signals at δ 6.48 (1H, d, J = 16 Hz, H-2″), 7.79 (1H, d, J = 16 Hz, H-3″), 7.51 (2H, d, J = 8 Hz, H-2‴, H-6‴), and 6.83 (2H, d, J = 8 Hz, H-3‴, H-5‴). A cross-peak between H-2 and C-1″ in the HMBC spectrum of **1** confirmed that the coumaroyl group is linked to C-2 of the piscidic acid moiety. The CD spectrum of **1** gave similar Cotton effects to those of fukinolic acid, for which the stereochemistry was elucidated earlier by synthetic work.[15] The absolute configuration of **1** was determined as 2*S*, 3*R* from the positive Cotton effects at 283 nm (+1100) and 228 nm (+5100) in the CD spectrum.[8] Thus, the structure of cimicifugic acid K (**1**) was established as shown.

Cimicifugic acid L (**2**) was isolated as a pale brown powder. The molecular formula was established as $C_{22}H_{22}O_{10}$ on the basis of the HRFABMS data ($[M - H]^-$ ion at *m*/*z* 445.1130). The ^{1}H and ^{13}C NMR data of **2** were similar to those of cimicifugic acid G.[13] However, the ^{1}H NMR spectrum of **2** indicated the presence of a *p*-hydroxybenzyl moiety at δ 7.09 (2H, d, J = 8 Hz, H-2′, H-6′) and 6.67 (2H, d, J = 8 Hz, H-3′, H-5′), showing typical AB-type proton signals at δ 2.99 and 3.10 (each 1H, d, J = 14 Hz) and an oxymethine proton signal at δ 5.66 (1H, s). In the HMBC experiment, ^{1}H−^{13}C long-range correlations were found between two methoxy protons (δ 3.89, 3.87) and C-3‴ and C-4‴. The CD spectrum of **2** also showed positive Cotton effects at 321 nm (+1500), 279 nm (+2300), and 229 nm (+14 300). The absolute configulation of **2** was deduced to be 2*S*, 3*R*.

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Table 1. NMR Spectroscopic Data (400 MHz) for Compounds **1**−**3**

	1 (cimicifugic acid K)			**2** (cimicifugic acid L)			**3** (cimicifugic acid M)		
position	δ_H (J in Hz)	δ_C	HMBC (H to C)	δ_H (J in Hz)	δ_C	HMBC (H to C)	δ_H (J in Hz)	δ_C	HMBC (H to C)
1		170.4			170.6			171.9	
2	5.66 (s)	77.5		5.66 (s)	77.7	1, 1″, 3, 4, 5	5.68(s)	77.7	
3		80.0			80.1			80.0	
4	2.99 (brd, 14)	42.0		2.99 (d, 14)	42.0	1′, 2, 2′, 3, 6′	3.09 (d, 14)	40.5	
	3.09 (brd, 14)			3.10 (d, 14)		1′, 2, 2′, 3, 6′	3.19 (d, 14)		
5		174.7			174.8			175.6	
1′		127.3			127.3			137.1	
2′	7.09 (d, 7)	132.5	4′, 6′	7.09 (d, 8)	132.6	3′, 4, 4′, 6′	7.28 (brd, 6)	131.7	4′, 6′
3′	6.66 (d, 7)	115.8	1′, 4′, 5′	6.67 (d, 8)	115.8	1′, 4′, 5′	7.22 (dd, 7, 6)	128.9	1′, 5′
4′		157.4			157.3		7.18 (brt, 7)	127.6	2′, 6′
5′	6.66 (d, 7)	115.8	1′, 3′, 4′	6.67 (d, 8)	115.8	1′, 3′, 4′	7.22 (dd, 7, 6)	128.9	1′, 3′
6′	7.09 (d, 7)	132.5	2′, 4′	7.09 (d, 8)	132.6	2′, 4, 4′, 5′	7.28 (brd, 6)	131.7	2′, 4′
1″		168.2			168.0			168.3	
2″	6.48 (d, 16)	114.3	1″, 1‴	6.56 (d, 16)	115.6	1″, 1‴, 3″	6.41 (d, 16)	114.5	1″
3″	7.79 (d, 16)	147.9	1″, 2″, 2‴, 6‴	7.81 (d, 16)	147.7	1″, 1‴, 2″, 2‴, 6‴	7.70 (d, 16)	148.0	1″, 2‴, 6‴
1‴		127.3			128.8			127.8	
2‴	7.51 (d, 8)	131.4	3″, 3‴, 4‴, 6‴	7.27 (d, 2)	111.8	1‴, 3″, 3‴, 4‴, 6‴	7.10 (d, 2)	115.3	3‴, 4‴, 6‴
3‴	6.83 (d, 8)	115.8	1‴, 2‴, 4‴, 5‴		150.9			146.8	
4‴		161.5			153.1			149.7	
5‴	6.83 (d, 8)	115.8	1‴, 3‴, 4‴, 6‴	6.09 (d, 8)	112.8	1‴, 3‴, 4‴	6.80 (d, 8)	116.6	3‴, 4‴, 6‴
6‴	7.51 (d, 8)	131.4	2‴, 3″, 4‴, 5‴	7.23 (dd, 8, 2)	124.3	2‴, 3″, 4‴	7.00 (dd, 8, 2)	123.2	1‴, 2‴, 4‴
OMe				3.89 (s)	56.5	3‴			
OMe				3.87 (s)	56.5	4‴			

Cimicifugic acid M (**3**) was isolated as a pale brown powder. The molecular formula was established as $C_{20}H_{18}O_9$ on the basis of the HRFABMS data ([M − H]$^-$ ion at m/z 401.0875). The molecular formula of **3** was consistent with that of compound **1**, although the ^{1}H and ^{13}C NMR spectra of the two compounds were slightly different. While compound **1** contains a piscidic acid moiety with a *p*-hydroxybenzene group, compound **3** showed the presence of a benzene ring, from the resonances at δ 7.28 (2H, brd, J = 6 Hz, H-2′, H-6′), 7.22 (2H, dd, J = 7, 6 Hz, H-3′, H-5′), and 7.18 (1H, brt, J = 7 Hz, H-4′). Significant differences in the ^{13}C NMR chemical shifts of C-1′ between compounds **1** and **3**, at δ 127.3 and 137.1, respectively, suggested that a benzene ring was linked to C-4 in **3**. The absolute configuration of **3** was also deduced to be 2*S*, 3*R* from the CD spectrum, showing positive Cotton effects at 218 nm (+6300). On the basis of these observations, the structure of cimicifugic acid M was established as shown.

Cimicifugic acid N (**4**) was isolated as a pale brown powder. The molecular formula was established as $C_{22}H_{22}O_{11}$ on the basis of the HRFABMS data ([M − H]$^-$ ion at m/z 461.1081). The molecular formula of compound **4** was the same as that of cimicifugic acid G.[13] In addition, the ^{1}H and ^{13}C NMR spectroscopic data of **4** were analogous to those of cimicifugic acid G, a compound with a *trans* configuration. The ^{1}H and ^{13}C NMR spectra of **4** indicated the presence of a fukiic acid moiety, showing signals of methylene protons at δ 2.84 and 2.91 (each 1H, d, J = 14 Hz), an oxymethine proton signal at δ 5.56 (1H, s), a 1,2,4-trisubstituted benzene moiety at δ 6.70 (1H, d, J = 2 Hz, H-2′), 6.62 (1H, d, J = 8 Hz, H-5′), and 6.55 (1H, dd, J = 8, 2 Hz, H-6′), a methylene carbon signal (δ 42.1), an oxymethine carbon signal (δ 77.8), a quaternary carbon signal (δ 80.0), and two carboxyl carbon signals (δ 170.6 and 175.0). On the other hand, evidence of a 3,4-dimethoxycinnamic acid moiety was seen from signals at δ 6.03 (1H, d, J = 12.5 Hz, H-2″), 7.01 (1H, d, J = 12.5 Hz, H-3″), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 7.71 (1H, d, J = 2 Hz, H-2‴), 6.92 (1H, d, J = 8.5 Hz, H-5‴), and 7.22 (1H, dd, J = 8.5, 2 Hz, H-6‴) in the ^{1}H NMR spectrum. However, the value of the coupling constant (J = 12.5 Hz) between H-2″ and H-3″ of compound **4** was smaller than that reported (J = 15.9 Hz) for cimicifugic acid G.[12] From these observations, compound **4** was identified as a *cis* isomer of cimicifugic acid G. The absolute stereochemistry at C-2 and C-3 of compound **4** was determined to be 2*S* and 3*R* from the positive Cotton effects at 321 nm (+1500), 279 nm (+2300), and 229 nm (+14 300) in the CD spectrum.

Shomaside F (**5**) was isolated as a pale brown powder. The molecular formula was established as $C_{20}H_{20}O_{10}$ on the basis of the HRFABMS data ([M − H]$^-$ ion at m/z 419.0981). Compound **5** exhibited similar spectroscopic future features to 3,4-dihydroxyphenyl-(6-*O*-benzoyl)-*O*-β-D-glucopyranoside, which has been isolated and characterized from *Protea eximia* (Knight) Fourc.[16] The ^{1}H and ^{13}C NMR spectra of **5** showed the presence of a 2,5-dihydroxybenzoic acid moiety linked to a β-D-glucopyranosyl moiety, giving a ROE between the proton signals at δ 7.56 (1H, d, J = 3 Hz, H-2) and the anomeric proton (H-1′) as well as between the proton signal at δ 7.24 (1H, dd, J = 9, 3 Hz, H-6) and the anomeric proton (H-1′). A long-range ^{1}H−^{13}C correlation between a carboxy carbon and an aromatic proton (H-2) in the HMBC spectrum suggested the presence of a 2,5-dihydroxybenzoic acid moiety. Consequently, the structure of compound **5** was established as shown.

In this study, in order to investigate the biological activities of cimicifugic acids K−N (**1**−**4**), their effects on hyaluronidase inhibitory activities were measured. Table 4 shows the 50% inhibition concentration (IC_{50}) values. As a result, inhibition was observed by cimicifugic acids K−N (**1**−**4**), which showed more potent inhibitory activities than rosmarinic acid.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO P-2200 digital polarimeter. UV spectra were measured in methanol on a JASCO V-630 spectrometer. Circular dichroism spectra were measured on AVIV model 215S spectrometer. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on an α-400 FT-NMR spectrometer, and chemical shifts are given as δ values with TMS as the internal standard at 35 °C in methanol-d_4. Inverse-detected heteronuclear correlations were measured using HMQC (optimized for $^1J_{C-H}$ = 145 Hz) and HMBC (optimized for $^nJ_{C-H}$ = 8 Hz) pulse sequences with a pulse field gradient. HRFABMS data were obtained on a JEOL JMS 700 mass spectrometer in the negative ion mode using an *m*-nitrobenzyl alcohol matrix. Preparative HPLC was performed on a JASCO 800 instrument.

Plant Material. The aerial parts of *Cimicifuga simplex* were obtained at Yamagata, Japan, in October 2006. The aerial parts of *Cimicifuga japonica* were harvested from the medical plant garden, University of Shizuoka, in October 2007. Voucher specimens (*Cimicifuga simplex*, 20061030; *Cimicifuga japonica*, 20071120) have been deposited at the Herbarium of the University of Shizuoka. These two plants were identified by Prof. Akira Ueno, University of Shizuoka.

Table 2. NMR Spectroscopic Data (400 MHz) for Compound **4**

	4 (cimicifugic acid N)			
position	δ_H (*J* in Hz)	δ_C	HMBC (H to C)	ROE (H to H)
1		170.6		
2	5.56 (s)	77.8	1, 1″, 3, 5	
3		80.0		
4	2.84 (d, 14)	42.1	1′, 2′, 3, 6′	
	2.91 (d, 14)		1′, 2′, 3, 5, 6′	
5				
1′		128.1		
2′	6.70 (d, 2)	118.8	4, 4′, 6′	
3′		145.3		
4′		145.7		
5′	6.62 (d, 8)	116.0	1′, 4′	
6′	6.55 (dd, 8, 2)	123.1	2′, 4, 4′	
1″		167.2		
2″	6.03 (d, 12.5)	116.8	1″, 1‴, 3″	
3″	7.01 (d, 12.5)	146.2	1″, 2‴, 6‴	
1‴		129.2		
2‴	7.71 (d, 2)	115.0	3″, 3‴, 4‴, 6‴	
3‴		149.8		
4‴		152.0		
5‴	6.92 (d, 8.5)	112.1	1‴, 3‴, 4‴	
6‴	7.22 (dd, 8.5, 2)	126.3	2‴, 3″, 4‴, 5‴	
OMe		56.6		2‴
OMe		56.6		5‴

Table 3. NMR Spectroscopic Data (400 MHz) for Compound **5**

	5 (shomaside F)			
position	δ_H (*J* in Hz)	δ_C	HMBC (H to C)	ROE (H to H)
1		150.9		
2	7.56 (d, 3)	119.3	1, 4, 6, 7	
3		113.7		
4		158.8		
5	6.72 (d, 9)	118.8	1, 3, 4	
6	7.24 (dd, 9, 3)	127.2	1, 2, 4	
COOH		172.9		
1″		131.3		
2″	7.98 (dd, 7.5, 1.5)	130.6	4″, 6″, 7″	
3″	7.45 (dd, 7.5, 1.5)	129.5	1″, 5′	
4″	7.60 (tt, 7.5, 1.5)	134.3	2′, 6″	
5″	7.45 (dd, 7.5, 1.5)	129.5	1″, 3‴	
6″	7.98 (dd, 7.5, 1.5)	130.6	2″, 4″, 7″	
7″		167.9		
sugar				
Glc 1	4.83 (d, 7.5)	103.4	1	2, 6
Glc 2	3.49 (m)	74.9	glc 1, glc 3	
Glc 3	3.51 (m)	77.9	glc 2	
Glc 4	3.46 (m)	72.1	glc 3	
Glc 5	3.75 (ddd, 7.5, 7.5, 2.5)	75.5		
Glc 6	4.42 (dd, 11.5, 7.5)	65.5	glc 5, 7″	
	4.70 (overlapped)		7″	

Table 4. Hyaluronidase Inhibitory Activities (IC_{50} μM) of Isolated Fukiic Acid Derivatives

compound	IC_{50}, μM
1	255
2	102
3	173
4	120
caffeic acid	>2000
ferulic acid	>2000
isoferulic acid	>2000
rosmarinic acid	545

Extraction and Isolation. The dried aerial parts of *C. simplex* (2.4 kg) were extracted twice with water−acetone (20:80) (20 L) under reflux for 4 h. The extract was concentrated under reduced pressure to give a dark brown, gummy residue (534 g). A 125 g portion of the residue was suspended in hot water (20 L). This suspension was passed through a porous polymer gel (Mitsubishi Diaion HP-20) column (10 × 30 cm), eluting with MeOH−H_2O (40:60) and MeOH. The fraction that eluted with MeOH−H_2O (40:60) was concentrated under reduced pressure to give a brown residue (14.9 g). A 4.0 g sample of the MeOH−H_2O extract was subjected to preparative HPLC [column, Tosoh TSKgel ODS-80Ts 5.5 × 120 cm; solvent, 0.1% trifluoroacetic acid−CH_3CN (90:10−70:30) linear gradient, UV 320 nm] to give 56 fractions (Frs. 1−56). The 86:14 solvent gave Fr. 14 [caffeic acid (91 mg)], the 83:17solvent gave Fr. 26 [fukinolic acid (241 mg)], the 82:18 solvent gave Fr. 27 [ferulic acid (165 mg)], the 78:22 solvent gave Fr. 42 [cimicifugic acid D (78 mg)], the 73:23 solvent gave Fr. 44 [isoferulic acid (19 mg)], the 76:24 solvent gave Fr. 41 [cimicifugic acid B (19 mg)] and Fr. 46 [cimicifugic acid E (69 mg)], and the 74:26 solvent gave Fr. 52 [cimicifugic acid E (69 mg)]. The 83:17 solvent gave Fr. 26 (72 mg), which was subjected to semipreparative HPLC [column, Develosil C30-UG-5, 2 × 25 cm; solvent, 0.1% trifluoroacetic acid−CH_3CN (75:25), UV 320 nm] to give 3,4-dimethoxycinnamic acid (2 mg). The 77:23 solvent gave Fr. 45 (30.8 mg), which was subjected to semipreparative HPLC [column, Develosil C30-UG-5, 2 × 25 cm; solvent, 0.1% trifluoroacetic acid−CH_3CN (75:25), UV 320 nm] to give Frs. 45-1−45-3. Fr. 45-1 (14.9 mg) was subjected to semipreparative HPLC [column, Cosmosil 5C_{18}-AR-II, 2 × 25 cm; solvent, 0.1% trifluoroacetic acid−CH_3CN (80:20), UV 320 nm] to give cimicifugic acid I (9 mg). The 75:25 solvent gave Fr. 50 (21 mg), which was subjected to semipreparative HPLC [column, Develosil C30-UG-5, 2 × 25 cm; solvent, 0.1% trifluoroacetic acid−CH_3CN (75:25), UV 320 nm] to give cimicifugic acid K (**1**) (1.5 mg). The 73:27 solvent gave Fr. 53 (22 mg), which was subjected to preparative HPLC [column, Sephadex LH-20, 2.5 × 100 cm; solvent, MeOH, UV 320 nm] to give cimicifugic acid N (**4**) (3.1 mg). The 72:28 solvent gave Fr. 54 (39 mg), which was subjected to preparative HPLC [column, Sephadex LH-20, 2.5 × 100 cm; solvent, MeOH, UV 320 nm] to give Frs. 54-1−54-3. Fr. 54-3 (19 mg) was subjected to semipreparative HPLC [column, Develosil C30-UG-5, 2 × 25 cm; solvent, 0.1% trifluoroacetic acid−CH_3CN (70:30), UV 320 nm] to give cimicifugic acid M (**3**) (5.5 mg). The 70:30 solvent gave Fr. 56 (15 mg), which was subjected to preparative HPLC [column, Sephadex LH-20, 2.5 × 100 cm; solvent, MeOH, UV 320 nm] to give cimicifugic acid L (**2**) (1.8 mg).

The dried aerial parts of *C. japonica* (320 g) were extracted twice with water−acetone (20:80) (2.5 L) under reflux for 2 h. The extract was concentrated under reduced pressure to give a dark brown, gummy residue (56 g). The residue was suspended in hot water (0.7 L) and extracted with ether continuously for 7 h and extracted with ethyl acetate continuously for 24 h. The water layer was fractionated over Mitsubishi Diaion HP-20 (400 g), eluting with water and MeOH. The fraction eluted with MeOH was concentrated under reduced pressure to give a brown residue (7.37 g). The MeOH eluate (3.5 g) was subjected to preparative HPLC [column, Tosoh TSKgel ODS-80Ts 5.5 × 120 cm; solvent, 0.1% trifluoroacetic acid−CH_3CN (95:5−63:37) linear gradient, UV 320 nm] to give 55 fractions (Frs. J1−J55). The 88:12 solvent gave Fr. J19 [caffeic acid (16 mg)], the 82:18 solvent gave Fr. J28 [ferulic acid (13 mg)], the 80:20 solvent gave Fr. J36 [fukinolic acid (897 mg)], the 77:23 solvent gave Fr. J43 [cimicifugic acid C (11 mg)], the 76:24 solvent gave Fr. J45 [cimicifugic acid A (19 mg)], and the 74:26 solvent gave Fr. J49 [cimicifugic acid E (21 mg)] and Fr. J52 [cimicifugic acid M (**3**) (10 mg)]. The 75:25 solvent gave Fr. J47 (11 mg), which was subjected to semipreparative HPLC [column, Cosmosil 5PE-MS, 2 × 25 cm; solvent, 0.1% trifluoroacetic acid−CH_3CN (77.5:22.5), UV 320 nm] to give cimicifugic acid K (**1**) (0.4 mg). The 74:26 solvent gave Fr. J48 (14 mg), which was subjected to semipreparative HPLC [column, Cosmosil 5PE-MS, 2 × 25 cm; solvent, 0.1% trifluoroacetic acid−CH_3CN (72.5:27.5), UV 320 nm] to give cimicifugic acid L (**2**) (0.5 mg). The 74:26 solvent gave Fr. J48 (21 mg), which was subjected to semipreparative HPLC [column, Cosmosil 5PE-MS, 2 × 25 cm; solvent, 0.1% trifluoroacetic acid−CH_3CN (77.5:22.5), UV 320 nm] to give shomaside F (**5**) (1.1 mg) and cimicifugic acid I (1.1 mg).

Cimicifugic acid K (1): pale brown powder, $[\alpha]_D^{24}$ +52.1 (*c* 0.24, MeOH); UV (MeOH) λ_{max} (log ε) 226 (4.40), 316 (4.40) nm; CD [θ] (*c* 0.72 mM, MeOH) (nm) +1100 (283), +5100 (228); ^{1}H NMR and ^{13}C NMR, Table 1; HRFABMS *m*/*z* 401.0907 (calcd for $C_{20}H_{18}O_9$−H, 401.0873).

Cimicifugic acid L (2): pale brown powder, $[\alpha]_D^{22}$ +43.2 (*c* 1.03, MeOH); UV (MeOH) λ_{max} (log ε) 259 (3.76), 322 (3.23) nm; CD [θ] (*c* 0.72 mM, MeOH) (nm) +1500 (321), +2300 (279), +14 300 (229); ^{1}H NMR and ^{13}C NMR, Table 1; HRFABMS *m*/*z* 445.1130 (calcd for $C_{22}H_{22}O_{10}$−H, 445.1135).

Cimicifugic acid M (3): pale brown powder, $[\alpha]_D^{24}$ +15.5 (*c* 0.42, MeOH); UV (MeOH) λ_{max} (log ε) 304sh (3.80), 330 (3.88) nm; CD [θ] (*c* 0.66 mM, MeOH) (nm) +6300 (218); ^{1}H NMR and ^{13}C NMR, Table 1; HRFABMS *m*/*z* 401.0875 (calcd for $C_{20}H_{18}O_9$−H, 408.0873).

Cimicifugic acid N (4): pale brown powder, $[\alpha]_D^{22}$ +31.3 (*c* 0.99, MeOH); UV (MeOH) λ_{max} (log ε) 220 (4.31), 325 (4.24) nm; CD [θ] (*c* 0.72 mM, MeOH) (nm) +1500 (321), +2300 (279), +14 300 (229); ^{1}H NMR and ^{13}C NMR, Table 2; HRFABMS *m*/*z* 461.1081 (calcd for $C_{22}H_{22}O_{11}$−H, 461.1084).

Shomaside F (5): pale brown powder, $[\alpha]_D^{24}$ −64.3 (*c* 0.28, MeOH); UV (MeOH) λ_{max} (log ε) 229 (4.24), 274 (3.27), 282 (3.30), 321 (3.60) nm; ^{1}H NMR and ^{13}C NMR, Table 3; HRFABMS *m*/*z* 419.0981 (calcd for $C_{20}H_{20}O_{10}$−H, 419.0978).

Assay of Inhibitory Effects on Hyaluronidase.[13] Inhibitory effects on hyaluronidase of the new compounds **1**−**4**, caffeic acid, ferulic acid, and isoferulic acid were checked by the same method reported in the previous paper[13] using rosmarinic acid as a positive control (Table 4).

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of new compounds are available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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