CONSTITUTIONS OF FORSYTHOSIDES F AND G, NEW PHENOL GLYCOSIDES OF FORSYTHIA VIRIDISSIMA STEMS+

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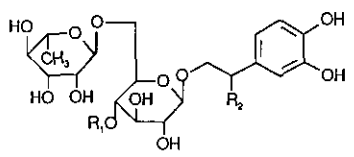
Abstract —— Two new phenol glycosides forsythoside F (1) and forsythoside G (2) have been isolated from Forsythia viridissima stems and their structures were established based on the spectroscopic data and chemical transformations. D-2-O-methylapiose was for the first time characterized in the natural product.

The crude drug Forsythiae Fructus is prescribed in the Oriental medicine as an antiinflammatory, a diuretic, a drainage or an antidote. Recent investigations have proven that the original plants of the drug contain a series of phenol glycosides which are primarily responsible to the antibacterial activity. Thus F. viridissima Lindley yielded forsythoside B (3) in the stems and acteoside (4) in the leaves,[1,2] while F. suspensa Vahl. afforded forsythoside A (5) in the leaves and forsythosides A, C (6), D (7) and E (8) in the fruits.[3] The result indicates further that F. viridissima is characterized by the presence of 3-rhamnosylglucose derivatives which contrasts to the 6-rhamnosylglucose derivatives in F. suspensa.

Our continued efforts to the investigation of pharmacologically active constituents resulted in isolation of two new phenol glucosides from F. viridissima stems, designated as forsythoside F (1) and forsythoside G (2) both having the 3-rhamnosylglucose part structure, and this article deals with their structure determination.

Forsythoside F (1), amorphous solid, $[\alpha]_D$ -70.9° (MeOH), exhibited the ion peaks at m/z 757 ($[M+1]^+$) and 779 ($[M+Na]^+$), corresponding to the molecular formula of $C_{34}H_{44}O_{19}$, in the FAB-mass spectrum. Further, the ^1H nmr spectrum (CD_3OD) of **1** displayed signals for a rhamnosyl group (δ 1.08 3H d, J 6Hz; 5.15 1H d, J 2Hz), a phenethyl group (δ 2.77 2H t, J 7Hz; 6.5-7.3 3H m), a β-glucosyl group (δ 4.36 1H d, J 8Hz) a caffeoyl group (δ 6.25 and 7.56 1H each d, J 16Hz; 6.5-7.3 3H m) and one more aldosyl group (δ 4.22 1H d, J 7Hz). All of the structural feafures are very similar to those of forsythosid B (3) except the signal at δ 4.22 which



5 R_1 = Caffeoyl R_2 = H
6 R_1 = Caffeoyl R_2 = OH
7 R_1 = H R_2 = OH
8 R_1 = R_2 = H

+ In the memories of Professor Emeritus Tetsuji Kametani.

Table I. ^{13}C Signals of Sugar Carbons in Forsythoside F and the Related Compounds

		Forsythoside F	Acteoside	β-Xyloside	Porsythoside B
β-Glucosyl	C-1	103.9 (d 158)	104.0 (d)		103.9 (d)
	2	73.8 (d)	73.7 (d)		73.7 (d)
	3	80.4 (d)	80.3 (d)		79.6 (d)
	4	70.1 (d)	70.3 (d)		70.3 (d)
	5	74.5 (d)	76.1 (d)		74.3 (d)
	6	69.2 (t)	62.1 (t)		68.2 (t)
α-Rhamnosyl	C-1	103.0 (d 170)	102.9 (d)		102.9 (d)
	2	72.4 (d)	72.4 (d)		72.3 (d)
	3	72.4 (d)	72.4 (d)		72.3 (d)
	4	75.6 (d)	75.7 (d)		75.5 (d)
	5	70.2 (t)	70.1 (t)		70.2 (t)
	6	19.1 (q)	19.0 (q)		19.0 (q)
Pentosyl	C-1	105.5 (d 157)		105.6 (d)	111.0 (d)
	2	74.9 (d)		74.7 (d)	77.7 (d)
	3	78.0 (d)		77.8 (d)	80.3 (s)
	4	70.9 (d)		71.1 (d)	75.0 (t)
	5	67.0 (t)		66.8 (t)	65.3 (t)

Chemical shift δ (ppm) from TMS in pyridine-$\underline{d}_5$; multiplicity and coupling constant in parenthesis

differs from the data for the β-apiosyl group (δ 4.91 1H $\underline{d}$, $\underline{J}$ 2.5Hz).[1] Corresponding differences are also observed between the ^{13}C nmr spectra of **1** and **3**, where the new signals at δ 105.5 ($\underline{d}$), 74.9 ($\underline{d}$), 78.0 ($\underline{d}$), 70.9 ($\underline{d}$) and 67.0 ($\underline{t}$) are assignable most likely to a β-xylosyl group (Table I).[4]

These analyses were substantiated by the following experiments. Thus acetylation of **1** with acetic anhydride in pyridine at room temperature overnight yielded the undecaacetate **1a** ($\underline{m/z}$ 1218).

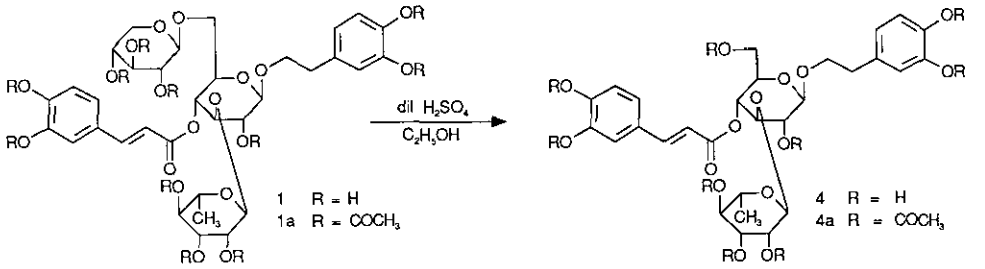


Table II. Selected ^1H Signals of Forsythoside F Acetate and the Related Compounds

Forsythoside F acetate (**1a**)	1.03 (d 6)	1.86, 1.92, 1.95, 1.99, 2.01, 2.01, 2.08, 2.25, 2.27, 2.28, 2.29 (all s)	2.84 (t 7)	4.33 (d 8), 4.49 (d 8), 5.00 (d 2)
F-Hydrolysate acetate (**1b**)	1.03 (d 6)	1.86, 1.93, 2.01, 2.08, 2.09, 2.25, 2.27, 2.28, 2.30 (all s)	2.85 (t 7)	4.37 (d 8), 5.02 (d 2)
Acteoside acetate (**4a**)	1.03 (d 6)	1.85, 1.93, 2.01, 2.07, 2.09, 2.26, 2.27, 2.29, 2.30 (all s)	2.85 (t 7)	4.37 (d 8), 5.02 (d 2)
Forsythoside A acetate (**5a**)	1.17 (d 6)	1.90, 1.93, 1.95, 1.95, 2.09, 2.25, 2.27, 2.28, 2.30 (all s)	2.85 (t 7)	4.49 (d 8), 4.77 (d 2)

Chemical shift δ (ppm) from TMS in $CDCl_3$; multiplicity and coupling constant in parenthesis

On the other hand, partial hydrolysis of **1** with 2N sulfuric acid in 50% aqueous ethanol at the refluxing temperature for 1h furnished its dexylosyl derivative (**4** 35%), which was then acetylated similarly to the peracetate. The product did not coincide to the forsythoside A nonaacetate (**5a**) but identical to the acteoside nonaacetate (**4a**) (Table II).

Thus the β-xylosyl group was allocated on the C-6 of the glucose moiety, and consequently, the structure of forsythoside F was assigned as β-(3,4-dihydroxyphenyl)ethyl 4-caffeoyl-3-α-rhamnosyl-6-β-xylosylglucoside (**1**).

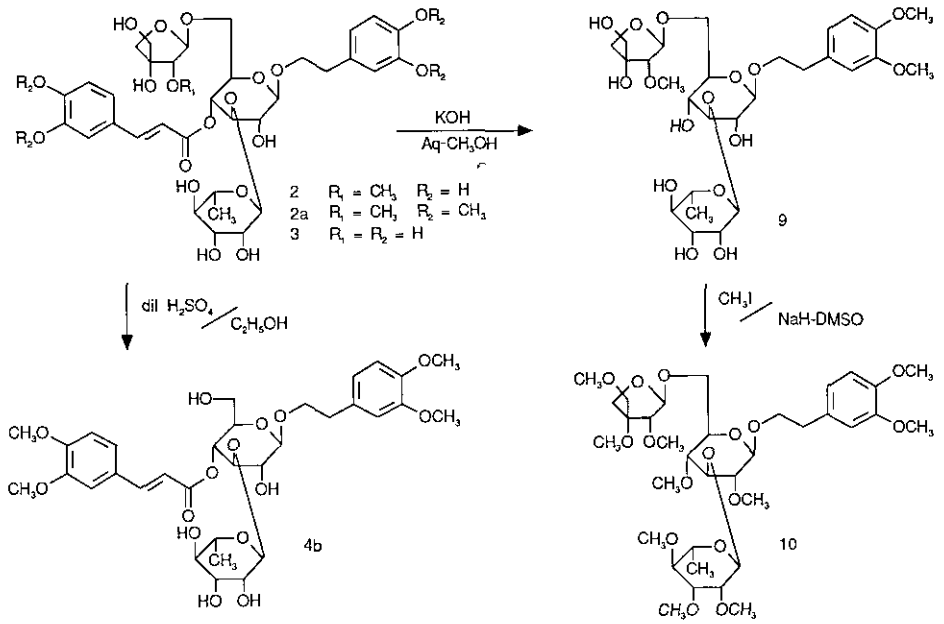
Forsythoside G (**2**) was isolated as its tetramethyl ether (**2a**), amorphous solid, $[\alpha]_D$ -69.1° (MeOH), from a crude forsythoside B fraction treated with methyl iodide and potassium carbonate in acetone. The largest ion peak of **2a** at m/z 825 ($[M-1]^+$) in the FD-mass spectrum indicated the molecular formula of $C_{39}H_{54}O_{19}$. The ^1H nmr peaks of **2a** (CD_3OD) at δ 1.09 (3H d, J 6Hz), 2.89 (2H t, J 7Hz), 3.41 (3H s), 3.78 (3H s), 3.82 (3H s), 3.84 (3H s), 3.85 (3H s), 4.37 (1H d, J 8Hz), 4.97 (1H d, J 2Hz), 5.19 (1H d, J 1Hz), 6.41 (1H d, J 16Hz), 6.8-7.3 (6H m), 7.67 (1H d, J 16Hz) and ^{13}C nmr spectrum (Table III) were very similar to those of forsythoside B (**3**) with additional signals at δ 3.41 (3H s) and 58.8 (1C q) compatible to an extra methoxyl group.

On hydrolysis with 2N sulfuric acid in aqueous ethanol, **2a** yielded acteoside tetramethyl ether (**4b** 30%), while reaction with potassium hydroxide in methanol, it gave the deacyl derivative (**9**), $[\alpha]_D$ -68.9°(MeOH). **9** was then methylated exhaustively with metyl iodide and sodium hydride in DMSO to furnish the permethyl ether (**10**), m/z 736, $[\alpha]_D$ -52.9° (MeOH), being identical to the product obtained by the same treatment of **3**.[1] Further, the C-2 carbon signals for the apiose moieties in

Table III. ^{13}C Signals of Sugar Carbons in Forsythoside G and the Related Compounds

		Forsythoside G tetramethyl ether (**2a**)	Deacylforsythoside G dimethyl ether (**9**)	Forsythoside B tetramethyl ether (**3a**)	Deacylforsythoside B dimethyl ether
β-Glucosyl	C-1	103.9 (d)	104.0 (d)	103.9 (d)	104.2 (d)
	2	73.6 (d)	73.9 (d)	73.7 (d)	74.0 (d)
	3	80.2 (d)	83.7 (d)	80.1 (d)	83.5 (d)
	4	70.9 (d)	70.0 (d)	70.8 (d)	70.0 (d)
	5	74.1 (d)	76.7 (d)	74.4 (d)	76.9 (d)
	6	68.2 (t)	68.8 (t)	68.3 (t)	68.6 (t)
α-Rhamnosyl	C-1	102.9 (d)	102.8 (d)	102.9 (d)	102.8 (d)
	2	72.3 (d)	72.4 (d)	72.4 (d)	72.6 (d)
	3	72.3 (d)	72.3 (d)	72.4 (d)	72.5 (d)
	4	75.5 (d)	75.1 (d)	75.6 (d)	75.3 (d)
	5	70.1 (t)	69.8 (t)	70.2 (t)	69.8 (t)
	6	18.9 (q)	18.4 (q)	18.8 (q)	18.6 (q)
β-Apiosyl	C-1	110.8 (d)	108.9 (d)	110.9 (d)	111.0 (d)
	2	86.7 (d)	86.5 (d)	77.8 (d)	77.7 (d)
	3	80.6 (s)	80.5 (s)	80.3 (s)	80.4 (s)
	4	75.0 (t)	74.9 (t)	75.0 (t)	74.9 (t)
	5	65.1 (t)	65.1 (t)	65.3 (t)	65.3 (t)
Methoxyl		58.8 (q)	58.7 (q)		

Chemical shift δ (ppm) from TMS in pyridine-d_5; multiplicity in parenthesis



the ^{13}C nmr spectra of **2a** and **9** showed apparent down field shifts due to alkylation (Table III), and hence, the structure of new sugar was assigned as 2-O-methylapiose.

Consequently, the structure of forsythoside G was established as β-(3,4-dihydroxyphenyl)ethyl 4-caffeoyl-6-β-(2-O-methyl)apiosyl-3-α-rhamnosylglucoside (**2**).

ACKNOWLEDGEMENTS

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NOTE AND REFERENCES

1) K. Endo, K. Takahashi, T. Abe, and H. Hikino, Heterocycles, 1982, **19**, 261.

2) The plant previously assigned as Forsythia koreana [1] was incorrect, and it should read Forsythia viridissima. Analysis of lignan derivatives also supported this identification.[5]

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4) T. Takemoto, S. Arihara, T. Nakajima, and M. Okuhira, Yakugaku Zasshi, 1983, **103**, 173.

5) S. Nishibe, M. Chiba, and S. Hisada, Shoyakugaku Zasshi, 1977, **31**, 131.

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