A New Mevalonolactone Glucoside Derivative from the Bark of *Prunus buergeriana*

Hiroko SHIMOMURA, Yutaka SASHIDA,* Yoshihiro MIMAKI, Tokuo ADACHI and Kiyoshi YOSHINARI

Tokyo College of Pharmacy, 1432–1, Horinouchi, Hachioji, Tokyo 192–03, Japan. *Received September 20, 1988*

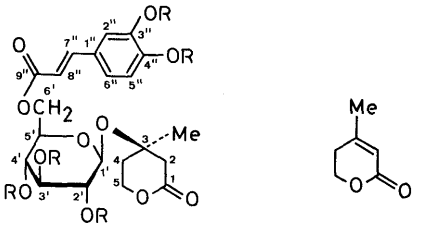
Phytochemical examination of the bark of *Prunus buergeriana* has led to the isolation of a new phenylpropanoid ester of mevalonolactone glucoside. The structure has been deduced from the results of chemical degradation and extensive nuclear magnetic resonance spectral experiments as (3*R*)-3-methyl-3-(6-*O*-caffeoyl-β-D-glucopyranosyloxy)-pentan-5-olide.

Keywords *Prunus buergeriana*; Rosaceae; mevalonolactone glucoside; phenylpropanoid glucoside; caffeic acid; bark

Some plants of the genus *Prunus* (Rosaceae) find a use in medicine. The barks of the subgenus *Cerasus* are used for the treatment of cough in Japan, whereas those of the subgenus *Padus* are mainly used in Europe and America. The species of the genus *Prunus* are particularly rich in flavonoids, but our examinations have shown the barks of *Prunus grayana* and *P. buergeriana* (belonging to the subgenus *Padus*) to be devoid of flavonoids.[1] On the other hand, phenylpropanoid glucosides have been isolated from the barks of both plants as characteristic constituents, some of which appear to be new derivatives.[1] Additional research on the bark of *P. buergeriana* has resulted in the isolation of a new phenylpropanoid ester of mevalonolactone glucoside (**1**). In this paper, the structure of the new constituent is presented and discussed.

Compound **1**, isolated from the methanol extract of the bark of *P. buergeriana*, had the molecular formula $C_{21}H_{26}O_{11}$ [secondary ion mass spectrum (SI-MS), *m/z* 455 $[M+H]^+$]. It gave a dark green coloration on adding ferric chloride reagent. The infrared (IR) spectrum showed the presence of hydroxyl group(s) (3392 cm^{-1}), carbonyl group(s) (1703 cm^{-1}), a double bond (1632 cm^{-1}) and a benzene ring (1605 and 1518 cm^{-1}). The proton nuclear magnetic resonance (^{1}H-NMR) spectrum exhibited three aromatic protons as an ABC system and two olefinic protons as an AX system whose coupling constant, $J=15.9$ Hz, indicated a *trans* geometry. In addition, the ultraviolet (UV) spectrum of **1** (methanol) exhibited absorptions at 244 nm (shoulder (sh)), 301 nm (sh) and 327 nm. The bathochromic shift at 327 to 373 nm upon addition of sodium methoxide reagent indicated the presence of two free vicinal phenolic hydroxyl groups.[2] Thus, the existence of a caffeoyl moiety in **1** was evident. On acetylation with acetic anhydride in pyridine, **1** afforded a pentaacetate (**1a**) whose IR spectrum showed no hydroxyl absorption. The electron impact mass spectrum (EI-MS) of **1a** revealed a peak at *m/z* 655 $[M+H]^+$, and the ^{1}H-NMR spectrum exhibited the existence of three aliphatic and two aromatic acetoxyl groups. Alkaline treatment of **1** with 3% sodium methoxide in methanol yielded D-glucose, methyl caffeate and 3-methyl-2-penten-5-olide (**1b**), which was formed by dehydration at the expense of the hydroxyl group from the C-3 position of the mevalonolactone. In the ^{1}H-NMR spectrum of **1**, the anomeric proton was observed at δ 4.52 with a coupling constant, $J=7.8$ Hz, confirming the anomeric center to be β-form, whereas the anomeric carbon appeared at δ 98.7 in the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum, which suggested that the glucopyranosyl moiety was linked to the quaternary carbon of the mevalonolactone residue through an oxygen atom. On the basis of these findings, **1** might be the caffeoyl ester of mevalonolactone glucoside. The mevalonolactone glucoside, that is, mevaloside, was previously isolated from the leaves of *Mespilus germanica*.[3] The site of the caffeoyl linkage to the sugar moiety could be readily determined from the ^{13}C-NMR data: the signal due to the β-D-glucose C-6 moved downfield to δ 64.8, accompanied with an upfield shift of the C-5 signal (δ 75.2).[1] Hence, the caffeoyl function is attached to the C-6 hydroxyl group. The above conclusion was also supported by the appearance of the deshielded H-6 proton signals in the ^{1}H-NMR spectrum at δ 4.49 (1H, dd, $J=11.8$, 2.2 Hz) and 4.24 (1H, dd, $J=11.8$, 6.7 Hz).[1b] The absolute configuration of the mevalonolactone C-3 was presumed to be *R* since all of the naturally occurring mevalonic acids have *R* configuration. The structure of **1** was thus formulated as (3*R*)-3-methyl-(6-*O*-caffeoyl-β-D-glucopyranosyloxy)pentan-5-olide.

There is general agreement that the C–O–CO–C group is planar in δ-lactones and accordingly the δ-lactone ring exists in boat and half-chair conformations.[4] The possibility of the boat form of **1** was ruled out because of the observation of the W-shaped long-range coupling between



	R
1	H
1a	Ac

1b

Chart 1

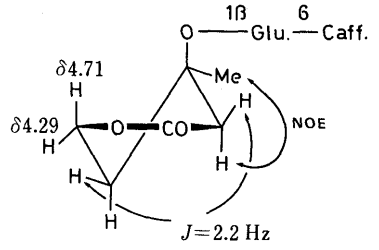


Chart 2

the H-2 equatorial proton and the H-4 equatorial proton in the ^{1}H-NMR spectrum (J=2.2 Hz). In the two-dimensional nuclear Overhauser effect correlation spectroscopy (2D NOESY) spectrum, a cross peak was observed between the C-3 methyl group and the H-2 axial proton of the mevalonolactone moiety. Furthermore, the H-5 axial proton resonated at lower field than the H-5 equatorial proton.[5] Thus, the conformation of the mevalonolactone residue was established to be as shown in Chart 2.

Mevalonic acid is an important intermediate in the synthesis of secondary plant metabolites such as terpenes and steroids. Glucosides of mevalonolactone, however, rarely occur in the plant kingdom[3] and this is the first report of a mevalonolactone glucoside with a phenylpropane moiety.

Experimental

IR spectra were recorded on a Perkin-Elmer 1710 FT-IR instrument, UV spectra on a Hitachi 557 spectrometer, and MS on a Hitachi M-80 machine. Optical rotations were measured with a JASCO DIP-360 automatic polarimeter. NMR spectra are taken with a Bruker AM-400 spectrometer. Chemical shifts were expressed in ppm (δ) values relative to the internal standard, tetramethylsilane (TMS), and the abbreviations used are as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet; br, broad. Column chromatographies were carried out on Fuji Davison silica gel BW-300 (200—400 mesh, Fuji Davison Co., Ltd.) and Sephadex LH-20 (25—100 μm, Pharmacia Fine Chemicals Co., Ltd.). Thin-layer chromatography (TLC) was performed on precoated Kieselgel 60 F_{254} plates (0.25 mm thick, Merck) and preparative TLC on precoated Kieselgel 60 F_{254} plates (0.5 mm thick, Merck), and spots were visualized under UV light (254 nm) irradiation and by spraying 10% H_2SO_4 solution followed by heating.

Isolation Details of the extraction and isolation procedure were described in the previous paper.[1c]

(3*R*)-3-Methyl-3-(6-*O*-caffeoyl-β-D-glucopyranosyloxy)pentan-5-olide (1) A pale-yellow amorphous powder (270 mg), $[\alpha]_D^{23}$ +13.6° (c=0.50, H_2O). UV λ_{max}^{MeOH} nm (log ε): 244 sh (3.96), 301 sh (4.12), 327 (4.22). UV $\lambda_{max}^{MeOH+3\%NaOMe}$ nm: 261, 311, 373. IR ν_{max}^{KBr} cm^{-1}: 3392 (OH), 2965, 2923 (CH), 1703 (C=O), 1632 (CH=CH), 1605, 1518 (aromatic ring), 1447, 1287, 1166, 1073, 1026, 930, 858, 811. SI-MS m/z (%): 455 $[M+H]^+$ (3), 325 (8), 163 (100), 113 (23). EI-MS m/z (%): 112 (38), 82 (100), 54 (35), 39 (47), 28 (25). ^{1}H-NMR (CD_3OD) δ: 7.59 (1H, d, J=15.9 Hz, H-7″), 7.04 (1H, d, J=2.0 Hz, H-2″), 6.95 (1H, dd, J=8.1, 2.0 Hz, H-6″), 6.77 (1H, d, J=8.1 Hz, H-5″), 6.30 (1H, d, J=15.9 Hz, H-8″), 4.71 (1H, ddd, J=11.2, 11.2, 3.9 Hz, H-5 axial), 4.52 (1H, d, J=7.8 Hz, H-1′), 4.49 (1H, dd J=11.8, 2.2 Hz, H-6′a), 4.29 (1H, ddd, J=11.2, 5.4, 3.1 Hz, H-5 equatorial), 4.24 (1H, dd, J=11.8, 6.7 Hz, H-6′b), 3.55 (1H, ddd, J=9.0, 6.7, 2.2 Hz, H-5′), 3.40 (1H, dd, J=9.0, 9.0 Hz, H-3′), 3.30 (H-4′, overlapping with solvent signals), 3.19 (1H, dd, J=9.0, 7.8 Hz, H-2′), 2.90 (1H, dd, J=17.6, 2.2 Hz, H-2 equatorial), 2.53 (1H, d, J=17.6 Hz, H-2 axial), 2.09 (1H, dddd, J=14.5, 3.9, 3.1, 2.2 Hz, H-4 equatorial), 1.94 (1H, ddd, J=14.5, 11.2, 5.4 Hz, H-4 axial), 1.38 (3H, s, Me (C-3)). ^{13}C-NMR (CD_3OD) δ: 173.2 (C-1), 169.1 (C-9″), 149.5 (C-4″), 147.1 (C-7″), 146.7 (C-3″), 127.8 (C-1″), 123.0 (C-6″), 116.6 (C-5″), 115.3 (C-8″), 115.1 (C-2″), 98.7 (C-1′), 78.1 (C-3′), 75.6 (C-3), 75.2 (C-5′), 74.9 (C-2′), 71.9 (C-4′), 67.2 (C-5), 64.8 (C-6′), 43.6 (C-2), 34.8 (C-4), 26.0 (Me (C-3)).

Acetylation of 1 A solution of **1** (20.0 mg) in Ac_2O and pyridine was allowed to stand at room temperature overnight. After addition of H_2O, the solution was extracted twice with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and dried over anhydrous Na_2SO_4 followed by evaporation to dryness under reduced pressure. The crude product was chromatographed on silica gel with *n*-hexane–acetone (2:1) and *n*-hexane–EtOAc (2:3) as the solvent systems to give a white amorphous powder, 20.5 mg (**1a**). IR ν_{max}^{KBr} cm^{-1}: 2928 (CH), 1752, 1721 (C=O), 1640 (CH=CH), 1505 (aromatic ring), 1431, 1375, 1324, 1251, 1220, 1176, 1115, 1041, 986, 908. EI-MS m/z (%): 665 $[M+H]^+$ (weak), 662 (weak), 580 (10), 535 (3), 510 (2), 492 (10), 450 (30), 408 (5), 390 (7), 348 (28), 306 (40), 288 (50), 247 (28), 205 (67), 180 (37), 163 (100), 134 (56), 113 (45), 82 (43), 44 (100). ^{1}H-NMR ($CDCl_3$) δ: 7.68 (1H, d, J=16.0 Hz, H-7″), 7.45 (1H, dd, J=8.4, 2.0 Hz, H-6″), 7.39 (1H, d, J=2.0 Hz, H-2″), 7.22 (1H, d, J=8.4 Hz, H-5″), 6.44 (1H, d, J=16.0 Hz, H-8″), 5.24 (1H, dd, J=9.5, 9.5 Hz, H-3′), 5.05 (1H, dd, J=9.5, 9.5 Hz, H-4′), 4.98 (1H, dd, J=9.5, 7.9 Hz, H-2′), 4.70 (1H, d, J=7.9 Hz, H-1′), 4.54 (1H, ddd, J=11.0, 11.0, 4.0 Hz, H-5 axial), 4.36 (1H, dd, J=12.2, 2.5 Hz, H-6′a), 4.28 (1H, ddd, J=11.0, 5.2, 3.5 Hz, H-5 equatorial), 4.23 (1H, dd, J=12.2, 6.2 Hz, H-6′b), 3.77 (1H, ddd, J=9.5, 6.2, 2.5 Hz, H-5′), 2.92 (1H, dd, J=17.6, 2.0 Hz, H-2 equatorial), 2.44 (1H, d, J=17.6 Hz, H-2 axial), 2.31, 2.30 (each 3H, s, arom. Ac), 2.04, 2.03, 2.01 (each 3H, s, Ac), 2.02 (H-4 equatorial, overlapping with acetoxyl signals), 1.88 (1H, ddd, J=14.5, 11.0, 5.2 Hz, H-4 axial), 1.35 (3H, s, Me (C-3)).

Alkaline Hydrolysis of 1 Compound **1** (30.0 mg) was treated with 3% NaOMe–MeOH at room temperature for 2 h. The reaction solution was passed through a cation exchange resin (Amberlite IR-120B) and the eluate was concentrated to give a residue. The crude hydrolysate, after dilution with H_2O, was extracted with $CHCl_3$, and the extract was subjected to silica gel column chromatography using *n*-hexane–acetone (2:1) to yield methyl caffeate (8.0 mg), identified by comparison with an authentic sample (TLC, Rf 0.49, $CHCl_3$–acetone (4:1)), and a colorless oil (**1b**) (2.0 mg). Compound **1b** was identified as 3-methyl-2-penten-5-olide. ^{1}H-NMR ($CDCl_3$) δ: 5.82 (1H, m, H-2), 4.38 (2H, t, J=6.3 Hz, H-5), 2.38 (2H, br t, J=6.3 Hz, H-4), 2.00 (3H, br s, Me (C-3)). ^{13}C-NMR ($CDCl_3$) δ: 158.1 (C-1), 130.3 (C-3), 117.2 (C-2), 66.3 (C-5), 29.6 (C-4), 23.3 (Me (C-3)). The aqueous residue was purified by silica gel column chromatography with $CHCl_3$–MeOH–H_2O (2:1:0.5) to yield D-glucose as a colorless viscous syrup (9.4 mg), $[\alpha]_D^{23}$ +46.8° (c=0.47, H_2O), TLC, Rf 0.28 (*n*-BuOH–acetone–H_2O (4:5:1)).

Acknowledgements We would like to thank Mr. Y. Shida and Miss Y. Kaneko for the MS measurements, and Mrs. C. Sakuma for measurements of the 2D NOESY spectrum. The assistance of Miss M. Tanaka and Miss Y. Tsuji in the experimental work is gratefully acknowledged.

References

1) *a*) H. Shimomura, Y. Sashida and T. Adachi, Phytochemistry, **26**, 249 (1987); *b*) *Idem, ibid.*, **26**, 2363 (1987); *c*) *Idem, ibid.*, **27**, 641 (1988).
2) M. F. Lahloub, G.-A. Gross, O. Sticher, T. Winkler and H.-R. Schulten, *Planta Medica*, **52**, 352 (1986).
3) *a*) S. G. Stanimirovic and D. L. Stanimirovic, *Glasnik Hem. Drustva, Beograd*, **28**, 167 (1963) [*Chem. Abstr.*, **62**, 8117*a* (1965)]; *b*) D. L. Stanimirovic and S. G. Stanimirovic, *ibid.*, **28**, 173 (1963) [*Chem. Abstr.*, **62**, 8117*b* (1965)]; *c*) D. Stanimirovic, D. Nastic and S. Stanimirovic, *Arh. Farm.*, **14**, 283 (1964) [*Chem. Abstr.*, **62**, 1965*h* (1965)]; *d*) R. Tschesche, K. Struckmeyer and G. Wulff, *Chem. Ber.*, **104**, 3567 (1971).
4) *a*) J. F. McConnell, A. M. Mathieson and B. P. Schoenborn, *Tetrahedron Lett.*, **1962**, 445; *b*) A. M. Mathieson and J. C. Taylor, *ibid.*, **1961**, 590; *c*) K. K. Cheung, K. H. Overton and G. A. Sim, *Chem. Commun.*, **1965**, 634.
5) R. C. Sheppard and S. Turner, *Chem. Commun.*, **1968**, 77.