Phenylethanoid Glycosides from *Digitalis purpurea* and *Penstemon linarioides* with PKCα-Inhibitory Activity

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In a continuation of our search for potential tumor inhibitors from plants, it was found that the CH_2Cl_2−MeOH (1:1) extracts from *Digitalis purpurea* and *Penstemon linarioides* both showed PKCα-inhibitory bioactivity. Bioassay-directed fractionation of the extract from *D. purpurea* yielded the new, weakly active phenylethanoid glycoside 2-(3-hydroxy-4-methoxy-phenyl)-ethyl-*O*-(α-L-rhamnosyl)-(1→3)-*O*-(α-L-rhamnosyl)-(1→6)-4-*O*-*E*-feruloyl-β-D-glucopyranoside (**1**) together with the four known compounds calceolarioside A (**2**), calceolarioside B (**3**), forsythiaside (**4**), and plantainoside D (**5**). The extract from *P. linarioides* yielded the three known glycosides leucosceptoside A (**6**), acteoside (**7**), and poliumoside (**8**), together with the iridoid plantarenaloside (**9**). All of the isolated compounds, except compound **9**, showed inhibitory activity against PKCα with IC_{50} values (in μM) of 125 (**1**), 0.6 (**2**), 4.6 (**3**), 1.9 (**4**), 14.8 (**5**), 19.0 (**6**), 9.3 (**7**), and 24.4 (**8**).

As described in the previous paper in this series[1] we have added a screen for inhibitors of protein kinase C (PKC) to our yeast assays for DNA-damaging agents,[2] in as much as PKC has emerged as an attractive target for anticancer treatment.[3] A search of plant extracts for inhibitors of PKC indicated that the detanninated CH_2Cl_2−MeOH (1:1) extracts of both *Digitalis purpurea* L. (Scrophulariaceae) and *Penstemon linarioides* Gray (Scrophulariaceae) showed PKCα-inhibitory bioactivity, and therefore bioassay-directed fractionation was undertaken on both extracts.

D. purpurea is a well-known herb with a long history of medicinal use. It is the source of the important cardiac glycosides digitoxin, gitoxin, and gitaloxin and has been used medicinally for at least 200 years.[4] It also contains flavonoid glycosides and an anthraquinone.[5] Recently, certain phenylethanoids such as desrhamnosyl acteoside, forsythiaside, purpureaside A, and purpureaside B have been isolated from *D. purpurea*, and it has been reported that acteoside (verbascoside) shows PKCα-inhibitory activity.[6]

P. linarioides has been reported to contain more than 50 iridoid glycosides,[7] and various phenylethanoids such as martynoside,[8] orobanoside,[9] stansioside,[9] and acteoside[10] have been isolated from other plants of this genus. As noted above, acteoside has shown PKCα-inhibitory activity and also selectively inhibited aldose reductase and formation of the 5-lipoxygenase product 15-hydroxy-5,8,11,13-eicosastetraenoic acid (15-HETE) and LTB_4 in human peripheral polymorphonuclear leukocytes, as well as showing antibacterial and cytotoxic activities.[11]

The extracts of both plants were subjected to partition between various organic solvents and aqueous MeOH, and the bioactivity of each extract against PKCα was concentrated in the *n*-BuOH fraction. For *D. purpurea* 2.52 g of crude extract gave 1.14 g of active *n*-BuOH-soluble material with an IC_{50} of 11.7 μg/mL against PKCα, while for *P. linarioides* 2.27 g of crude extract yielded 1.27 g of *n*-BuOH-soluble material with an IC_{50} of 17.1 μg/mL against PKCα. Column chromatography of the *n*-BuOH fraction from *D. purpurea* on Si gel with the solvent CH_2Cl_2−MeOH−H_2O (8:2:0.1) gave seven fractions. The bioactive fraction 6 gave compound **1** (4.8 mg) and plantainoside (**5**) (8.0 mg) by preparative TLC on RP-18 plates with the solvent MeOH−H_2O (55:45) and repeated column chromatography on Si gel with the solvent CH_2Cl_2−MeOH−H_2O (8:2:0.1). Using the same conditions, calceolariside A (**2**, 16.8 mg), calceolariside B (**3**, 8.8 mg), and forsythiaside (**4**, 22.3 mg) were isolated from the bioactive fractions 2, 3, and 4, respectively.

In similar fashion, the *n*-BuOH fraction from *P. linarioides* was subjected to Si gel column chromatography with the solvents CH_2Cl_2−MeOH−H_2O (6:1 and 4:1). Fraction 4 yielded leucosceptoside A (**6**, 120 mg, 5.2%) by further Si gel column chromatography with the solvent CH_2Cl_2−MeOH (6:1). Fraction 6 gave acteoside (**7**, 145 mg, 6.4%) on purification by polyamide column chromatography, and fraction 8 gave poliumoside (**8**, 62.7 mg, 2.8%) and plantarenaloside (**9**, 36.8 mg, 1.6%) on Si gel column chromatography with the solvent CH_2Cl_2−MeOH−H_2O (8:2:0.1).

Compound **1** had the composition $C_{35}H_{50}O_{19}$ as determined by HRFABMS. Its ^{1}H NMR spectrum, with signals at δ 3.88 (3H, s), 7.20 (1H, d, J = 1.9 Hz), 6.81 (1H, d, J = 8.2 Hz), 7.08 (1H, dd, J = 1.9, 8.2 Hz), 6.38 (1H, d, J = 15.9 Hz) and 7.66 (1H, d, J = 15.9 Hz), and its UV spectrum, with λ_{max} at 289 and 330 nm, suggested the presence of a feruloyl moiety, while ^{1}H NMR signals at δ 6.73 (1H, d, J = 2.1 Hz), 6.83 (1H, d, J = 8.1 Hz), 6.69 (1H, dd, J = 2.1, 8.1 Hz), and 2.82 (2H, br t) indicated the presence of a phenethyl moiety. Compound **1** thus belongs to the class of phenylethanoid natural products. The ^{13}C NMR spectrum of **1**, in addition to signals attributable to the phenethyl and the feruloyl groups, contained signals for 18 carbons corresponding to the carbohydrate moiety. The signals in the ^{1}H NMR spectrum of **1** for the anomeric protons at δ 5.19 (1H, d, J = 1.4 Hz), 4.62 (1H, d, J = 1.5

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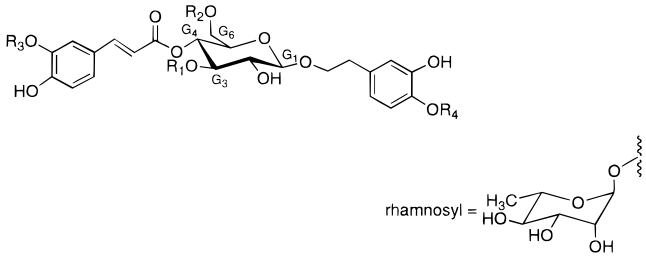
Table 1. NMR Data of Compound 1, Poliumoside (8), and Martynoside (10)

	compound **1**		poliumoside (**8**)	martynoside (**10**)[a]
	δ_H(J value in Hz)	δ_C	δ_C	δ_C
aglycon				
A-1		132.8	131.4	132.7
A-2	6.73 (d, 2.1)	117.1	117.1	117.0
A-3		147.6	146.1	147.1
A-4		147.3	144.7	147.2
A-5	6.83 (d, 8.1)	112.9	116.3	112.8
A-6	6.69 (dd, 2.1, 8.1)	121.2	121.3	121.1
A-7	2.82 (dt)	72.3	72.3	72.2
A-8		36.6	36.5	36.5
Caffeoyl−				
C-1		127.7	127.6	127.5
C-2	7.2 (d, 1.9)	111.8	115.2	111.9
C-3		149.4	146.8	150.4
C-4		150.8	149.8	149.1
C-5	6.81 (d, 8.2)	116.5	116.5	116.6
C-6	7.08 (dd, 1.9, 8.2)	124.4	123.2	124.2
C-7	7.66 (d. 15.9)	148.0	148.0	147.8
C-8	6.38 (d, 15.9)	115.1	114.7	115.1
−COOR		168.0	168.0	168.3
Glucosyl−				
G-1	4.38 (d, 7.9)	104.4	104.2	104.2
G-2		76.2	76.2	76.2
G-3		81.5	81.6	81.5
G-4		70.4	70.6	70.6
G-5		74.7	74.5	76.6
G-6		67.6	67.5	62.4
Rhamnosyl−1				
Rh′-1	5.19 (d, 1.7)	103.0	103.1	103.0
Rh′-2		72.3	72.4	72.3
Rh′-3		72.1	72.1	72.0
Rh′-4		73.9	73.9	73.8
Rh′-5		69.9	70.4	70.4
Rh′-6		18.4	18.4	18.4
Rhamnosyl−2				
Rh″−1	4.62 (d, 1.5)	102.3	102.3	
Rh″−2		72.3	72.3	
Rh″−3		72.0	72.0	
Rh″−4		73.7	73.7	
Rh″−5		69.9	69.9	
Rh″−6		18.0	18.0	
CH_3O−(Caff−3)	3.81 (s)	56.5		56.5
CH_3O−(Ag−4)	3.88 (s)	56.4		56.5

[a] Data from Miyase et al. 12c.

Hz), and 4.38 (1H, d, 7.9 Hz) and for the terminal methyl groups at δ 1.09 (3H, d, J = 6.1 Hz) and 1.19 (3H, d, J = 6.3 Hz) indicated that **1** contained two rhamnosyl units and one glucosyl unit.

Comparison of the NMR data of **1** with those of the known compound poliumoside (**8**) (Table 1) indicated that both carbon and proton chemical shifts of the sugar part of **1** were very similar to those of poliumoside (**8**). Compound **1** also had very similar ^{13}C NMR data to those of martynoside **10**,[12] after making adjustments for the fact that **10** has one rhamnose less than compound **1.** A careful comparison of the ^{13}C NMR data of **1** with the data of **10** showed that the only significant differences occurred at G_5 and G_6 in **1**, thus suggesting that the additional rhamnosylation in **1** took place at the G_6 position of **10**.[12] The long-range couplings between H−G_4 (δ_H 4.99) and −COOR (δ_C 168.0) in the HMBC spectrum of **1** indicated that the feruloyl group was connected at G_4 via an ester linkage, and the long-range couplings between H−Rh_1 (δ_H 5.19) and C−G_3 (δ_C 81.5) and between H−Rh′$_1$ (δ_H 4.62) and C−G_6 (δ_C 67.6) demonstrated that one rhamnosyl group was located at the G_6 and the other at the G_3 position. The correlation between H−G_1 (δ_H 4.38) and C-α (δ_C 72.3) indicated the location of the α-phenylethanyl glucoside moiety.



1		R_1 = rhamnosyl,	R_2 = rhamnosyl,	R_3 = CH_3,	R_4 = CH_3
2	(Calceolariodise A)	R_1 = H,	R_2 = H,	R_3 = H,	R_4 =H
4	(Forsythiaside)	R_1 = H,	R_2 = rhamnosyl,	R_3 = H,	R_4 = H
6	(Leucosceptoside)	R_1 = rhamnosyl,	R_2 = H	R_3 = CH_3,	R_4 = H
7	(Acteoside)	R_1 = rhamnosyl,	R_2 = H	R_3 = H,	R_4 = H
8	(Poliumoside)	R_1 = rhamnosyl,	R_2 = rhamnosyl,	R_3 = H,	R_4 = H
10	(Martynoside)	R_1 = rhamnosyl,	R_2 = H,	R_3 = CH_3,	R_4 = CH_3

In a NOESY spectrum, NOE correlations observed between the CH_3O− signal at δ_H 3.81 and the proton signal at δ_H 7.20 (1H, d, 2.1) showed this CH_3O− group to be located at the C-3 position of the feruloyl moiety. Similarly, the other CH_3O− group could be assigned to the C-4 position of the phenethyl group by the correlation between the CH_3O− signal at δ_H 3.88 (3H, s) and proton signal at δ_H 6.83 (1H, d, J = 8.1 Hz). Based on these data, **1** could be assigned as 2-(3-hydroxy-4-methoxyphenyl)-ethyl-*O*-(α-L-rhamnosyl)−(1→3)-*O*-(α−L-rhamnosyl)−(1→6)-4-*O*-*E*-feruloyl-*β*-D-glucopyranoside.

Compounds **2**−**9** were assigned as calceolarioside A,[13] calceolarioside B,[13] forsythiaside,[14] plantainoside D,[15] leucoceptoside,[12] acteoside,[9,12,13,16] poliumside,[17] and plantarenaloside,[17] respectively, by comparison of their ^1H and ^{13}C NMR, DQCOSY, HMQC, HMBC, and NOESY spectra with literature data. They also showed the same HRFABMS, $[\alpha]_D$, UV, and IR data with values in the literature. Calceolarioside A and plantarenaloside were also identified by direct comparison with authentic samples. Plantainoside D was isolated for the first time from *P. linarioides*.

All of the isolated compounds except compound **9** showed inhibitory activity against PKCα, with IC_{50} values (μM) of 125 (**1**), 0.6 (**2**), 4.6 (**3**), 1.9 (**4**), 14.8 (**5**), 19.0 (**6**), 9.3 (**7**) and 24.4 (**8**). The PKCα inhibitory bioactivities of **1**-**6** and **8** have not been reported previously in the literature.

Experimental Section

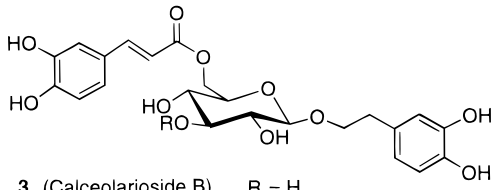
General Experimental Procedures. Optical rotations were recorded with a Perkin-Elmer 241 Polarimeter. UV spectra were measured on a Beckman DU-50 instrument and IR spectra on a Nicolet Impact 400 spectrophotometer. NMR spectra were recorded in CD_3OD on a Varian Unity 400 NMR instrument at 399.951 MHz for ^1H and 100.578 MHz for ^{13}C, using standard Varian pulse sequences. Exact mass measurements were obtained at the Nebraska Center for Mass Spectrometry. Other conditions were as previously described.[2]

Plant Material. Stems, leaves, and fruit of *Digitalis purpurea* L. (Scrophulariaceae) were collected on Norfolk Island in May 1965 (PR-9503, B633363), and the whole plant of *Penstemon linarioides* Gray (Scrophulariaceae) was collected in New Mexico. in June 1964 (PR-8513, B632569). Voucher specimens are on deposit in the Herbarium of the National Arboretum, Agricultural Research Service, U. S. D. A., Washington, DC. The dried samples were extracted with CH_2Cl_2-MeOH (1:1) to give 2.52 g of *D. purpurea* extract as HEX 652 and 2.27 g of *P. linarioide* extract as HEX 1216.

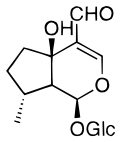
Isolation of Phenylethanoids 1−**5.** The CH_2Cl_2-MeOH extract HEX 652 (2.52 g) from *D. purpurea* was passed through a polyamide column (80 g, ICN Pharmaceuticals, Inc., Eschwege, Germany) to yield a detanninated fraction (2.16 g, PKCα IC_{50} = 78 μg/mL). After partition of the detanninated fraction between EtOAc and aqueous MeOH, followed by partition of the aqueous MeOH fraction between H_2O and

n-BuOH, a bioactive *n*-BuOH fraction (1.14 g, PKC_α $IC_{50} = 12$ μg/mL) was obtained. This was subjected to column chromatography on Si gel (60 g) with elution by CH_2Cl_2-MeOH−H_2O (8:2:0.1) to give seven fractions after combination of similar components as determined by TLC. Purification of active compounds from the bioactive fractions was achieved by preparative TLC on RP-18 with MeOH−H_2O (55:45) followed by column chromatography on Si gel with CH_2Cl_2-MeOH−H_2O (8:2:0.1). Fraction 2 yielded calceolarioside A (**2,** 16.8 mg, 0.67%); fraction 3 gave calceolarioside B (**3**, 8.8 mg, 0.35%); fraction 4 gave forsythiaside (**4**, 22.3 mg, 0.89%); fraction 6 gave plantainoside D (**5**, 8.0 mg, 0.32%) and the new natural product **1** (4.79 mg, 0.19%). The structures of compounds **2**-**5** were assigned by ^1H and ^{13}C NMR, DQCOSY, HMQC, HMBC, and NOESY spectra, and by HRFABMS, $[\alpha]_D$, UV, and IR. Calceolarioside A was also identified by direct comparison with an authentic sample.[13]

Isolation of Phenylethanoids 6−9. The CH_2Cl_2-MeOH (1:1) extract from *P. linarioides* was partitioned between EtOAc and aqueous MeOH, and the active aqueous MeOH fraction was then partitioned between H_2O and *n*-BuOH. The bioactive *n*-BuOH fraction (1.27 g, 56.1%, with $IC_{50} = 17.1$ μg/mL against PKCα) was subjected to column chromatography on Si gel with the solvent CH_2Cl_2-MeOH (6:1 and 4:1) to give 10 fractions, of which fractions 4, 6, and 8 showed PKCα-inhibitory activity. Leucosceptoside A (**6**, 120 mg, 5.2%) was isolated from fraction 4 by further Si gel column chromatography with the solvent CH_2Cl_2-MeOH (6:1). Acteoside (**7**, 145 mg, 6.4%) was purified by polyamide column chromatography of fraction 6, and poliumoside (**8**, 62.7 mg, 2.8%) and plantarenaloside (**9**, 36.8 mg, 1.6%) were obtained by Si gel column chromatography of fraction 8 with the solvent CH_2Cl_2-MeOH−H_2O
(8:2:0.1). The structures of compounds **6**-**8** were assigned by comparison of ^1H and ^{13}C NMR, NOESY, HMQC and HMBC spectra, and UV, MS, and $[\alpha]_D$ values with literature data; all data were identical to those published.[10,12,14,15,19] Plantarenaloside (**9**) was identified by direct comparison with an authentic sample (co-TLC, ^1H and ^{13}C NMR).



3 (Calceolarioside B) R = H
5 (Plantainoside D) R = Glucosyl



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Compound **1**: light yellow gum-like substance, $[\alpha]^{23}_D$ -60.4° (*c* 0.22, MeOH), UV (MeOH) λ_{max} (log ϵ) 218 (4.06), 235 sh (3.98), 289 (3.85), and 330 (4.05) nm; IR ν_{max} (KBr) 3600−3100 (OH), 1720 (conjugated COOR), 1600 (>C=C<); ^1H and ^{13}C NMR data see Table 1; FABMS *m*/*z* 805.3077 (calcd for $C_{37}H_{50}O_{19}Li$, 805.3106).

PKCα-Inhibitory Bioassay. Bioassay for inhibition of PKC was carried out as described previously.[1]

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