Dihydrostilbene Derivatives from *Glycyrrhiza glabra* Leaves

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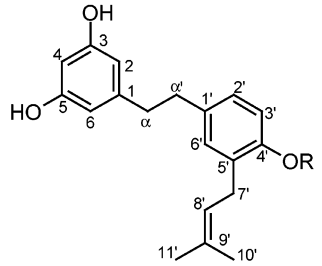
Four new dihydrostilbenes, α,α′-dihydro-3,5-dihydroxy-4′-acetoxy-5′-isopentenylstilbene (**1**), α,α′-dihydro-3,3′,4′-trihydroxy-5-*O*-isopentenyl-6-isopentenylstilbene (**2**), α,α′-dihydro-3,5,3′-trihydroxy-4′-methoxystilbene (**3**), and α,α′-dihydro-3,3′-dihydroxy-5*β*-D-*O*-glucopyranosyloxy-4′-methoxystilbene (**4**), together with seven known flavonoids, glabranin isomer, naringenin, lupiwighteone, pinocembrin 7-*O*-glucoside, astragalin, isoquercitrin, vicenin II, and the inositol, pinitol, were isolated from the leaves of *Glycyrrhiza glabra* grown in Sicily. The structures of **1**−**4** were elucidated by spectroscopic methods.

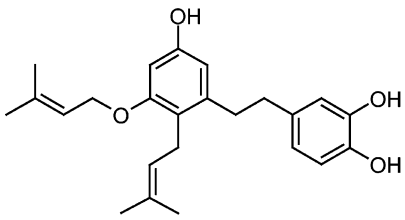
Licorice root, obtained from different species of the genus *Glycyrrhiza*, can be considered one of the oldest and most widely used "drugs" in the world,[1] being present in most pharmacopoeias of eastern and western countries. Innumerable properties are ascribed to *Glycyrrhiza* roots and are due to the triterpene saponin, glycyrrhizin (glycyrrhizinic acid), as well as to several phenolic constituents.[2] In contrast, the aerial parts of this plant have received scant interest.[3−5] Recently, we investigated a lipid extract of the leaves of Sicilian *G. glabra* and characterized five new dihydrostilbene derivatives together with four known flavonoids.[6] In a continuation of these studies, we have reinvestigated this lipid extract and have also examined butanol and methanol extracts of the leaves of *G. glabra*. Four new (**1**−**4**) dihydrostilbene derivatives, the first three from the lipid extract and the last from the butanolic extract, have been isolated and characterized, together with eight known metabolites, comprising flavonoids, flavonoid *O*-glycosides, a flavonoid *C*-glycoside, and pinitol, a well know inositol derivative.

Fresh leaves of *Glycyrrhiza glabra* were initially defatted with *n*-hexane, then extracted with ethyl acetate, and the residue was extracted with *n*-butanol. After filtration, the residue was subjected to extraction with methanol, as detailed in the Experimental Section.

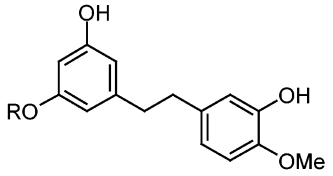
The first new compound, α,α′-dihydro-3,5-dihydroxy-4′-acetoxy-5′-isopentenylstilbene (**1**), was obtained as a yellow−orange oil. The molecular formula, $C_{21}H_{24}O_4$, was established by HREIMS ([M$^+$] 340.4191). The NMR data of this compound, listed in Table 1, closely resembled those of α,α′-dihydro-3,5,4′-trihydroxy-5′-isopentenylstilbene (**1a**) previously isolated from *G. glabra*.[6] The differences were due to the presence in the ^{1}H NMR spectrum of a signal at *δ* 2.30 (s, 3H) and two signals in the ^{13}C NMR spectrum at *δ* 170.3 (s) and 20.9 (q), suggesting that compound **1** is an acetyl derivative of **1a**. This was confirmed by the EIMS fragmentation pattern, which indicated the presence of an acetyl group, and from the IR spectrum which showed, besides the absorptions at 3687 and 3592 cm^{-1} (OH) and 1603 (benzenoids) that were superimposable with those of **1a**, a further absorption at 1757 cm^{-1}, characteristic of a carbonyl ester function. Finally, the position of the acetyl group was indicated by the chemical shifts of the B ring carbons, in particular, by the values of C-4′ (*δ* 146.9) and C-3′ (*δ* 121.8) compared with those of **1a**. The final confirmation of the substitution pattern, as well as of the whole structure, was provided by HMBC NMR correlations.



1 R = COCH$_3$
1a R = H



2



3 R = H
4 R = Glc

The second new compound, α,α′-dihydro-3,3′,4′-trihydroxy-5-*O*-isopentenyl-6-isopentenylstilbene (**2**), showed a molecular formula of $C_{24}H_{30}O_4$, as established by HREIMS ([M$^+$] 382.2141). The UV absorptions at 204, 222, and 279 nm, and those in the IR spectrum at 3687 and 3595 cm^{-1} (OH) and 1604 cm^{-1} (benzenoids), were typical of a dihydrostilbenoid. The aromatic region of the ^{1}H NMR and ^{1}H−^{1}H COSY spectra showed a signal at *δ* 6.21 (1H, d, *J* = 2.5 Hz) coupled with a signal at *δ* 6.24 (1H, d, *J* = 2.5 Hz). This indicated a meta-coupled system, characteristic of a tetrasubstituted benzene ring and was attributed to the A ring. The other aromatic system showed a signal at *δ* 6.41 (1H, dd, *J* = 1.8, 8 Hz) coupled to the protons at *δ* 6.63 (1H, d, *J* = 8 Hz) and *δ* 6.59 (1H, d, *J* = 1.8 Hz), characteristic of a 1,3,4-trisubstituted ring and attributable to the B ring. The presence of α,α′-methylene groups was confirmed by the signals at *δ* 2.62 (2H, m) and 2.60 (2H,

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Table 1. ^{1}H and ^{13}C NMR Data of Compounds **1**−**4**[a]

	1		**2**		**3**		**4**	
	δ_C	δ_H *J* (Hz)	δ_C	δ_H *J* (Hz)	δ_C	δ_H *J* (Hz)	δ_C	δ_H *J* (Hz)
1	144.2 s		118.0s		144.8 s		143.0 s	
2	108.5 d	6.08 d(2)	107.9 d	6.21 d (2.5)	106.7	6.22 d (2)	108.7 d	6.43 d (2)
3	156.7 s		155.9 s		158.2 s		159.0 s	
4	101.0 d	6.16 d (2)	98.1 d	6.24 d (2.5)	99.9 d	6.18 d (2)	110.1 d	6.38 d (2)
5	156.7 s		157.1 s		158.1 s		159.8 s	
6	108.5 d	6.08 d (2)	141.3 s		106.6 d	6.22 d (2)	101.8 d	6.39 d (2)
a	37.7 t	2.75 m	35.1 t	2.62 m	37.6 t	2.71 m	38.5 t	2.92 m
α′	36.9 t	2.75 m	36.5 t	2.60 m	36.5 t	2.71 m	37.5 t	2.92 m
1′	139.6 s		132.7 s		134.8 s		134.0 s	
2′	127.1 d	6.94 dd (2, 8)	115.6 d	6.59 d (1.8)	111.4 d	6.73 d (2)	112.9 d	6.72 d (2)
3′	121.8 d	6.92 d (8)	145.0 s		146.2 s		146.0 s	
4′	146.9 s		143.2 s		145.4 s		145.6 s	
5′	133.1 s		115.5 d	6.63 d (8)	115.0 d	6.83 d (8)	115.5 d	6.83 d (8)
6′	130.4 d	6.93 d (2)	118.8 d	6.41 dd (1.8, 8)	118.6 d	6.22 dd (2, 8)	120.0 d	6.63 dd (2, 8)
7			24.0 t	3.17 d (7)				
8			124.4 d	4.97 t (7)				
9			129.2 s					
10			17.9 q	1.68 s				
11			25.4 q	1.73 s				
7′	29.7 t	3.17 d (7.2)	64.5 t	4.41 d (7)				
8′	121.7 d	5.20 t (7.2)	120.4 d	5.40 t (7)				
9′	133.1 s		136.4 s					
10′	18.2 q	1.72 bs	17.9 q	1.67 s				
11′	26.1 q	1.67 bs	25.5 q	1.60 s				
CO	170.3 s							
CH_3	20.9 q	2.30 s						
OCH_3					55.2 q	3.88 s	56.2 q	3.79 s
Glc								
1							102.2 d	4.85 d (7.5)
2							74.6 d	3.02 m
3							77.9 d	3.04 m
4							71.3 d	3.01 m
5							77.5 d	3.05 m
6							62.6 t	3.81 dd (12, 2)
								3.70 dd (12, 5)

[a] The assignments were based on COSY, DEPT, HMQC, and HMBC experiments.

m). The remaining signals in the NMR spectra were ascribable to two isopentenyl moieties, with one bonded to an aromatic carbon and the other to an oxygen atom. In the first of these, the ^{1}H NMR spectrum showed signals at δ 3.17 (d, J = 7 Hz) and 4.97 (t, J = 7 Hz), ascribable to an allylic methylene and a vinyl proton, respectively, of a *C*-isopentenyl group. Instead, the second isopentenyl chain showed signals for an allylic methylene group at δ 4.41 (d, J = 7 Hz) and a vinyl proton at δ 5.40 (t, J = 7 Hz), confirming that, in this case, the methylene group was bonded to an oxygen atom. Moreover, the ^{1}H NMR spectrum showed signals related to four methyl groups at δ 1.73, 1.68, 1.67, and 1.60 (each 3H, s). The ^{13}C NMR spectrum and DEPT experiment showed the presence of nine quaternary carbons, seven methines, four methylenes, and four methyls. The HMBC and the NOE experiments allowed the positions of the isopentenyl groups to be established on the A ring. In particular, the signal at δ 3.17 related to two methylene protons showed long-range correlations with the signals for C-1, C-5, and C-6, whereas the other methylene proton (δ 4.41) showed long-range correlation with C-5. In the NOESY spectrum, this same methylene proton correlated with the aromatic proton at C-4 (δ 6.24), and this allowed its position to be established on the aromatic ring. This metabolite, unlike those isolated earlier from *G. glabra* leaves, showed a different substitution pattern in the A ring, due to the presence of a first isopentenyl moiety on an oxygen atom, whereas the second isopentenyl unit is at the C-6 position instead of C-4, as in all previous analogues.[6] Furthermore, this is the first *O*-isopentenyl dihydrostilbene derivative to have been found in *G. glabra*, and is similar to glepidotin D, isolated from *G. lepidota*.[3]

The third new compound, α,α′-dihydro-3,5,3′-trihydroxy-4′-methoxystilbene (**3**), exhibited the molecular formula of $C_{15}H_{16}O_4$, as established from its HREIMS ([M$^+$] 260.2896). The UV and IR absorptions (see Experimental Section) were very similar to those shown by **1** and **2**. The analysis of its NMR spectra clearly showed the absence of an isopentenyl chain. In fact, the ^{1}H NMR signals were only ascribable to two spin systems related to the corresponding two aromatic rings, the two methylenes forming the bridge of the dihydrostilbene structure, and a methoxyl group. The pattern of substitution of the two aromatic rings was established on the basis of the analysis of the two spin systems, with the first one being similar to that of compound **1** for ring A and the second one similar to that of compound **2** for ring B (Table 1). Finally, the position of the methoxy group at C-4′ was indicated by the HMBC NMR correlations.

The last new dihydrostilbene, α,α′-dihydro-3,3′-dihydroxy-5β-D-*O*-glucopyranosyloxy-4′-methoxystilbene (**4**), was isolated from the butanol extract of the leaves of *G. glabra*. The molecular formula, $C_{21}H_{26}O_9$, as indicated by the HRFABMS, was assigned to this compound. The UV spectrum exhibited maxima at 204, 226, and 280 nm, and the IR spectrum suggested the presence of hydroxy groups (3690 cm^{-1}). Both the ^{1}H and ^{13}C NMR data (Table 1) closely resembled analogous data for compound **3**. However, the presence of a glucopyranosyl moiety was evident, for which β-anomeric ^{1}H and ^{13}C NMR resonances appeared at δ 4.85 (d, J = 7.5 Hz) and δ 102.2 (d), four oxymethines

were seen between δ 3.05 and 3.01 (^{1}H), δ 77.9 and 71.3 (^{13}C), with one oxymethylene resonating at δ 3.81 (dd, 1H) and 3.70 (dd, 1H) in the ^{1}H NMR spectrum, and at δ 62.6 (t) in the ^{13}C NMR spectrum. HMQC and HMBC NMR experiments confirmed the substitution pattern of the molecule together with the exact position of the glucoside moiety. Definitive confirmation of the structure came from the enzymatic hydrolysis of compound **4** with β-glucosidase, which gave a compound that was indistinguishable from **3**, whereas the sugar unit was identified as D-(+)-glucose on the basis of the comparison of its TLC R_f value and optical rotation with an authentic sample.

Experimental Section

General Experimental Procedures. Melting points were determined using an LD Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a JASCODIP-370 digital polarimeter. UV and FTIR spectra were recorded on Perkin-Elmer model Lambda 25 and model Spectrum BX spectrophotometers, respectively. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 400 instrument, at 400 and 100 MHz, respectively. Multiplicities of ^{13}C resonances were determined by DEPT. NOESY, HMQC, and HMBC spectra were performed using standard Bruker software. HREIMS and HRFABMS were obtained at 70 eV on a Kratos M50S mass spectrometer. Thin-layer chromatography (TLC) was carried out using precoated silica gel F254 plates (Merck). Column and flash column chromatography were run on MN Polyamide SC6 < 0.07 mm, MN Polyamide SC6-Ac, 0.05−0.06 mm, silica gel 0.063−0.2 mm, Diol 40−63 μm, LiChroprep Si 60 25−40 μm, and 40−63 μm (Merck) as stationary phases, and JaiFlash System for flash chromatography (Gyan).

Plant Material. *Glycyrrhiza glabra* was collected on the banks of the Simeto river, Sicily, Italy, in May 2003, and identified by Mr. Felice Rao. A voucher specimen (#0037GG1) has been deposited in the Herbarium of the Department of Botany, Catania, Italy.

Extraction and Isolation. The fresh plant was ground and freeze-dried to obtain 550 g of dried material, which was defatted three times with hexane. The residual material was extracted with ethyl acetate, and after removing the extract by filtration, the material was further extracted with butanol. After filtration, the residual was finally extracted with methanol. All the extractions were done in triplicate, at room temperature with continuous stirring, and after evaporation of each solvent under reduced pressure, 100, 14, and 30 g of the ethyl acetate, butanol, and methanol extracts, respectively, were obtained.

A portion of the ethyl acetate extract (50 g) was then subjected to column chromatography over MN Polyamide SC 6. Elution with a stepwise gradient of MeOH−H_2O (70:30 → 100:0) to 100% ethyl acetate gave 17 fractions (A−S). Fraction G (790 mg) was chromatographed over a silica gel column using a gradient of MeOH−CH_2Cl_2 (3:97 → 10:90) for elution to give 15 fractions (1−15). Fraction 11 (32 mg) was purified over silica gel LiChroprep Si 60 25−40 μm using methyl ethyl ketone−CH_2Cl_2 (1:9) as eluent and afforded compound **3** (15 mg). Fraction L (2 g of 3.90 g) from the polyamide column was separated using Diol 40−63 μm with CH_2Cl_2−hexane (70:30 → 90:10) and then acetone−CH_2Cl_2 (3:97 → 5:95 → 100:0) to obtain eight fractions. Fraction 2 (250 mg) was purified by flash chromatography using Diol 25−40 μm as stationary phase and CH_2Cl_2−hexane (70:3) as eluent to give the glabranin isomer[7] (20 mg). From fraction 4 (340 mg), after flash column chromatography over Diol 40−63 μm with acetone−CH_2Cl_2 (3:97 → 5:95) as eluent, compound **2** (50 mg) was obtained. Fraction N (5.5 g) was subjected to column chromatography using acetylated polyamide, with acetone−hexane (13: 87 → 100:0) and then 100% MeOH as eluents. This afforded 15 fractions (1−15), and further purification of the sixth fraction over a JaiFlash chromatography system using a silica gel cartridge (35−70 μm) gave naringenin[8] (30 mg). Fraction S (7 g) was chromatographed over an acetylated polyamide column, with the eluents being acetone−hexane (40:60 → 100:0), MeOH−acetone (5:95), and 100% MeOH. Nine fractions were obtained, and the seventh (680 mg), after purification using a flash chromatography column over Diol 25−40 μm and acetone−hexane mixtures (15:85 → 17:83) as the eluents, yielded lupiwighteone[9] (35 mg) and compound **1** (50 mg).

The butanol extract (14 g) was chromatographed over polyamide, using as eluents, acetone−hexane (10:90 → 100:0), MeOH−acetone (10:90), MeOH (100%), and then H_2O−MeOH (1:1). This chromatographic fractionation yielded 13 fractions (A−O BuOH), with fraction M further chromatographed using Diol 40−63 μm with ethyl acetate (100%), acetone (100%), MeOH (100%), and H_2O (100%) as the eluents to afford nine fractions. The fifth fraction was purified using a flash Diol 40−63 μm chromatography column, with ethyl acetate (100%), acetone (100%), and MeOH (100%) as eluents to give five fractions. The second fraction (150 mg) was solubilized in a mixture of MeOH−ethyl acetate (7:93), and pinitol[10] (10 mg) was obtained as a white semisolid mass. After filtration, the solution was partitioned in H_2O and ethyl acetate. The aqueous fraction (80 g) was subjected to flash chromatography over Lichroprep 40−63 μm, using methyl ethyl ketone−ethyl acetate (60:40) and then MeOH (100%) for elution to give three fractions, the second of which gave compound **4** (50 mg). Fraction N (1.3 g), eluted from the polyamide column with MeOH−H_2O (1:1), was flash chromatographed using Lichroprep silica gel as stationary phase and methyl ethyl ketone−ethyl acetate (60:40) saturated with water as eluent; five fractions were obtained. The first (300 mg), third (280 mg), and fourth (500 mg) of these were chromatographed with silica gel as stationary phase and methyl ethyl ketone−ethyl acetate (15:85) saturated with water as eluent to obtain isoquercitrin[11] (5 mg), astragalin[12] (15 mg), and pinocembrin 7-*O*-glucoside[13] (50 mg), respectively.

A part of the methanol extract (15 g) was subjected to chromatographic fractionation on a polyamide column. Seven fractions (A−G MeOH) were obtained. Fraction A (9 g) was treated with a mixture of MeOH−ethyl acetate (1:1), and by precipitation and subsequent filtration, another portion of pinitol[10] (2.6 g) was purified. Fraction B (1.6 g) was subjected to the same process, and the precipitate (100 mg) was purified on a C_{18} reversed-phase column with MeOH−H_2O (30:70) as the eluent to obtain vicenin II[14] (70 mg).

α,α′-Dihydro-3,5-dihydroxy-4′-acetoxy-5′-isopentenylstilbene (1): yellow−orange oil (yield 0.018% fresh wt); UV (EtOH) λ_{max} (log ϵ) 203 (4.98), 226 sh (4.28), 277 (3.59) nm; IR (CH_2Cl_2) ν_{max} 3678, 3581, 3050, 2987, 1757, 1603, 1421, 1250 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS *m/z* 340 [M$^+$] (7), 297 (14), 175 (100), 157 (3), 133 (6), 123 (3) 119 (4); HREIMS *m/z* 340.4191 (calcd for $C_{21}H_{24}O_4$, 340.4191).

α,α′-Dihydro-3,5-dihydroxy-5-isopentenyl-6-*O*-isopentenylstilbene (2): orange−red oil (yield 0.018% fresh wt); UV (EtOH) λ_{max} (log ϵ) 204 (4.96), 222 (4.43), 279 (3.95) nm; IR (CH_2Cl_2) ν_{max} 3687, 3595, 3050, 2987, 1604, 1422, 1280, 1057 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS *m/z* 382 [M$^+$] (23), 314 (22), 192 (32), 161 (41), 123 (100), 69 (98); HREIMS *m/z* 382.2141 (calcd for $C_{24}H_{30}O_4$, 382.2141).

α,α′-Dihydro-3,5,3′-trihydroxy-4′-methoxystilbene (3): yellow oil (yield 0.005% fresh wt); UV (EtOH) λ_{max} (log ϵ) 203 (4.94), 227 (4.40), 281 (4.04) nm; IR (CH_2Cl_2) ν_{max} 3690, 3050, 2987, 1422, 1278, cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS *m/z* 260 (29), 227 (2), 137 (100), 122 (5), 94 (3), 77 (2); HREIMS *m/z* 260.2896 (calcd for $C_{15}H_{16}O_4$, 260.2896).

α,α′-Dihydro-3,3′-dihydroxy-5β-D-*O*-glucopyranosyloxy-4′-methoxystilbene (4): yellow oil (yield 0.009% fresh wt); $[\alpha]^{22}_D$ −0.26° (*c* 0.36, EtOH); UV (MeOH) λ_{max} (log ϵ) 204 (4.90), 228 (4.39), 280 (4.02) nm; IR (CH_2Cl_2) ν_{max} 3690, 3050, 2987,-1422, 1279 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; FABMS *m/z* 462 [M + K], 445 [M + Na], 422 [M$^+$]; HRFABMS *m/z* 422.4324 (calcd for $C_{21}H_{26}O_9$, 422.4320).

Enzymatic Hydrolysis of 4. Compound **4** (35 mg) was dissolved in water (2 mL), and β-glucosidase (35 mg) was added. The mixture was then shaken at 40 °C for 1 h. Methanol (1 mL) was added allowing the precipitation of enzyme, the mixture was centrifuged, and the methanolic layer, after evaporation of the solvent under reduced pressure, was purified over silica gel LiChroprep Si 60 25−40 μm using methyl ethyl ketone−CH_2Cl_2 (1:9) as eluent to afford 15 mg of a compound, whose physicochemical properties were indistinguishable from **3**. Further elution with MeOH−CH_2Cl_2 (25:75) gave a compound (8 mg) which was identified as glucose by comparative TLC with a standard using the MeOH−CH_2Cl_2 (4:6) solvent system and detection by spraying with the *p*-anisaldehyde−H_2SO_4 reagent. The D-configuration of the glucose was confirmed by its $[\alpha]^{22}_D$ value of +48.6° (*c* 0.50, H_2O).

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Supporting Information Available: Extraction procedure for all components, and structures of known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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