Resveratrol and Other Phenolics from the Bark of *Yucca schidigera* Roezl.

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Five phenolic constituents have been identified in *Yucca schidigera* bark, and their structures were established by spectral (FABMS and NMR) experiments. These included two known stilbenes, *trans*-3,4′,5-trihydroxystilbene (resveratrol) and *trans*-3,3′,5,5′-tetrahydroxy-4′-methoxystilbene, as well as three novel compounds, yuccaols A, B, and C, with spiro-structures rarely occurring in the plant kingdom. It is suggested that yuccaols A−C are biosynthethized via attachment of a stilbenic derivative to the carbocationic intermediate of the oxidative flavanone−flavonol conversion.

Keywords: *Yucca; Yucca schidigera; resveratrol; stilbenes; yuccaols A−C; phenolics*

INTRODUCTION

Yucca schidigera is a plant that grows widely in Mexico, and it is well-known because of its very high (10% of dry weight) content of steroidal saponins. The extract of this plant finds wide commercial application in foods and cosmetics and as a pharmaceutical additive (*1*). This is regarded as a "generally recognized as safe" (GRAS) product, approved by the Food and Drug Administration as a food additive. Yucca extract and powder have also been used for the reduction of ammonia and odors in poultry excreta on poultry farms (*2*).

Yucca is known to contain resveratrol (*trans*-3,4′,5-trihydroxystilbene) (*3*), a natural phytoalexin found in considerable amounts in the skin of grapes (*4* and *5*), mulberries and peanuts (*6*), and in some medicinal plants, including *Cassia quinquangulata* and *C. garrettiana* (*7*), *Erythropleum lasiantum* (*8*), *Ficus barteri* fruits (*9*), *Reynoutria japonica* (*10*), *Polygonum cuspidatum* (*11*), and *Smilax glabra* (*12*). Oxyresveratrol (piceatannol, 2,3′,4,5′-tetrahydroxystilbene) was found as a naturally occurring compound in *Morus alba* (*13*) and in *Scirpus maritimus* (*14*), gnetins, a resveratrol oligomers, were identified in *Gnetum* species (*15*) and resveratrol trimers were reported in *Sophora leachiana* (*16*).

The presence of resveratrol in some plant species was of no interest until 1992 when Siemann and Creasy (*17*) reported the occurrence of this compound as a potent antioxidant in red wine. It is believed that, because of its antioxidant activity, resveratrol is responsible, at least in part, for the reduced risk of cardiovascular disease in man from moderate consumption of red wine (*18*−*22*). Resveratrol also shows antimutagenic, antiviral (*23*), cancer chemopreventive (*24* and *25*), apoptosis induction (*26* and *27*), dioxin toxicity prevention (*28*), antiallergic (*29*), and phytoestrogen (*30*) activities.

These multifunctional activities of resveratrol encourage the search for structurally related compounds for possible pharmaceutical application. Thus, the aim of our present work was to search for phenolic constituents of yucca bark.

MATERIALS AND METHODS

Plant Material. Yucca (*Yucca schidigera*) bark was obtained from Desert King Int., Chula Vista, CA.

Chemicals. *trans*-Resveratrol was obtained from Sigma-Aldrich, St. Louis, MO.

Chromatography and Spectral Analysis. Phenolics were chromatographed on Cellulose (Merck) plates developed with 15% HOAc, and after drying were visualized under UV (366 nm). High-performance liquid chromatography was performed on an HPLC system (Waters, Milford, MA) consisting of a model 616 pump, a model 600s controller, and a model 996 photodiode array detector operating at 310 nm. The Millenium Chromatography Manager was used to monitor chromatographic parameters and to process the data. Separations were performed on a 5 μm (250 × 4.6 mm i.d.) Eurospher 80 C_{18} column (Säulentechnik, Germany). Chromatographic runs were carried out using a mobile phase (20% CH_3CN in 1% H_3PO_4→40% CH_3CN in 1% H_3PO_4 during 70 min.) linear gradient.

Melting points were uncorrected. The CD spectra were recorded in MeOH at 20 °C on a Jasco P-1020 spectropolarimeter. FABMS spectra were recorded on a MAT 95 (Finnigan) spectrometer with glycerol matrix and the ESI−HRMS was recorded on a Mariner Biospectrometry Workstation (Per Septive Biosystems). ^1H and ^{13}C NMR spectra in CD_3OD solutions were measured on a Bruker DRX-600 spectrometer operating at 599.19 MHz for ^1H and 150.86 MHz for ^{13}C. 2D experiments: $^1H-^1H$ DQF−COSY (double quantum filtered direct chemical shift correlation spectroscopy), inverse detected $^1H-^{13}C$ HSQC (heteronuclear single quantum coherence), HMBC (heteronuclear multiple bond connectivity) and ROESY (2D nOe in a rating frame) were obtained using UX-NMR software. IR measurements were obtained on a Bruker IFS-48 spectrometer.

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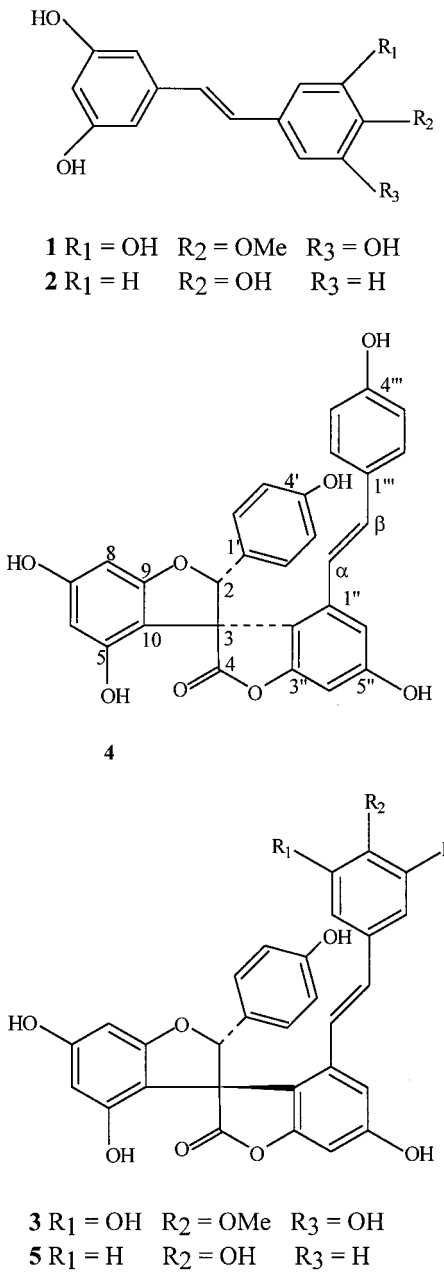


Figure 1. Compounds **1**-**5** from *Yucca schidigera* bark.

Extraction and Separation of Phenolics. Powdered yucca bark (100 g) was extracted at room temperature with MeOH (2 × 300 mL). After filtration the methanol was evaporated in vacuo at 40 °C yielding a brown solid (15.3 g). The solid was dissolved in 15% MeOH and loaded onto a C_{18} column (30 × 70 mm, 60 μm, Baker) equilibrated with water. The column was washed with 40% MeOH to remove phenolics and then with MeOH to wash out the remaining substances. The MeOH fraction was discarded after checking with HPLC that it did not contain any phenolic constituents. The 40% MeOH fraction was evaporated to dryness, redissolved in 20% CH_3CN in 1% H_3PO_4, and loaded onto a C_{18} column (40 × 300 mm, 25−40 μm, Merck). The column was washed with CH_3CN in H_3PO_4 (linear gradient 20−70% CH_3CN) and 10-mL fractions were collected. Fractions showing identical chromatographic characteristics (TLC and HPLC) were combined. All isolation and separation procedures were performed in the dark to avoid any isomerization of compounds. Five fractions containing single pure compounds were obtained.

Compound **1**, 0.042 g. FABMS: (-ve) *m/z* 273 $[M-H]^-$, 259 $[M\text{-}CH_2-H]^-$, 137 $[M-C_7O_3H_5-H]^-$; (+ve) 275 $[M+H]^+$. ^1H NMR: 6.86 (1H, d, J = 15.8 Hz, H-β), 6.81 (1H, d, J = 15.8 Hz, H-α), 6.57 (2H, s, H-2′,H-6′), 6.48 (2H, d, J = 1.5 Hz, H-2, H-6), 6.23 (1H, d, J = 1.5 Hz, H-4), 3.83 (3H, s, OCH_3). ^{13}C NMR: δ 159.0 (C-3, C-5), 151.2 (C-3′,C-5′), 140.4 (C-1), 136.2 (C-4′), 134.3 (C-1′), 129.0 (C-β), 128.4 (C-α), 106.6 (C-2′, C-6′), 105.6 (C-2, C-6), 103.0 (C-4), 60.5 (Me).

Compound **2**, 0.030 g. FABMS: (-ve) *m/z* 227 $[M-H]^-$, 137 $[M-C_6OH_3-H]^-$; (+ve) 229 $[M+H]^+$, 213 $[M\text{-}16+H]^+$. ^1H NMR: δ 7.37 (2H, d, J = 8.3 Hz, H-2′, H-6′), 6.99 (1H, d, J = 16.2 Hz, H-β), 6.85 (1H, d, J = 16.2 Hz, H-α), 6.84 (2H, d, J = 8.3 Hz, H-3′, H-5′), 6.47 (2H, d, J = 1.5 Hz, H-2, H-6), 6.19 (1H, d, J = 1.5 Hz, H-4). ^{13}C NMR: δ 159.4 (C-3, C-5), 158.5 (C-4′), 140.9 (C-1), 130.5 (C-1′), 129.3 (C-β), 128.9 (C-2′, C-6′), 127.8 (C-α), 116.5 (C-3′, C-5′), 105.7 (C-2, C-6), 103.1 (C-4).

Compound **3**, 0.204 g; amorphous powder; Mp 212−213 °C; $[\alpha]_D^{20}$ +20.8° (MeOH, c 0.1). HRMS *m/z* 541.1129 [Calcd for $C_{30}H_{21}O_{10}$ $(M)^-$: 541.1154]. FABMS: (-ve) *m/z* 541 $[M-H]^-$; (+ve) 543 $[M+H]^+$. IR ν^{KBr}_{max} cm^{-1}: 2923, 1782, 1620, 1515, 1465, 1257, 1172, 1134, 1076, 1022. For ^1H and ^{13}C NMR see Table 1.

Compound **4**, 0.145 g; amorphous powder; Mp 205−206 °C (with browning); $[\alpha]_D^{20}$ +78.4° (MeOH, c 0.1). HRMS *m/z* 495.1074 [Calcd for $C_{29}H_{19}O_8$ $(M)^-$: 495.1086]. FABMS: (-ve) *m/z* 495 $[M-H]^-$, 375 $[M-C_8OH_7-H]^-$; (+ve) 497 $[M+H]^+$. IR ν^{KBr}_{max} cm^{-1}: 2928, 1789, 1620, 1515, 1458, 1261, 1168, 1137, 1076, 1022. For ^1H and ^{13}C NMR see Table 1.

Compound **5**, 0.040 g; amorphous powder; Mp 209−210 °C (with browning); $[\alpha]_D^{20}$ +93.8° (MeOH, c 0.1). HRMS *m/z* 495.1067 [Calcd for $C_{29}H_{19}O_8$ $(M)^-$: 495.1086]. FABMS (-ve) *m/z* 495 $[M-H]^-$; (+ve) 497 $[M+H]^+$. IR ν^{KBr}_{max} cm^{-1}: 2925, 1782, 1621, 1515, 1465, 1250, 1169, 1134, 1076, 1026. For ^1H and ^{13}C NMR see Table 1.

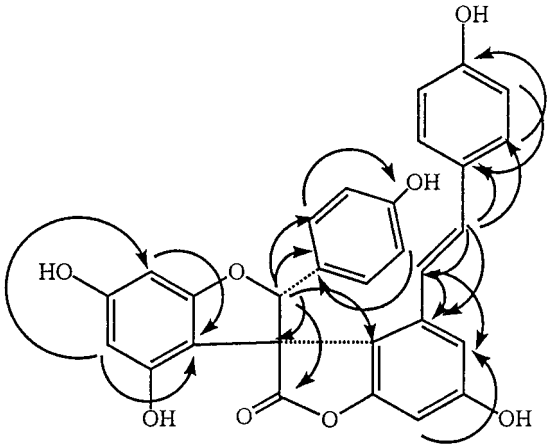


Figure 2. HMBC correlations of compound **4** (yuccaol A).

RESULTS AND DISCUSSION

Preliminary analyses with HPLC (diode array detection) of the methanol extract of yucca bark indicated that it contained some phenolic-like constituents. The column chromatography of this extract afforded five compounds, which were fully characterized with spectral techniques.

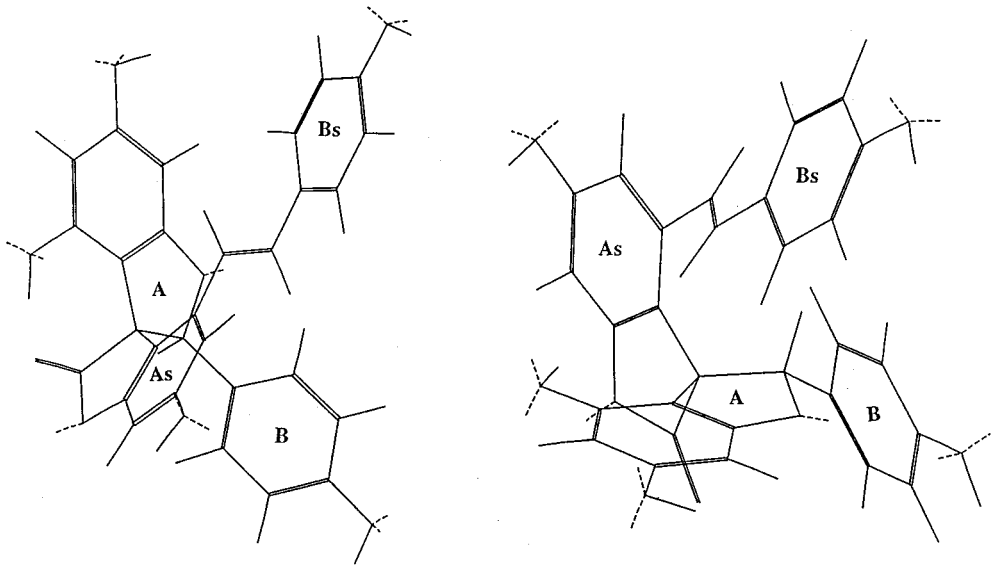
Thus, compound **2** showed a retention time value and UV absorption maxima (224 and 313 nm) identical to those obtained for authentic *trans*-resveratrol standard (*trans*-3,4′,5-trihydroxystilbene). The identity of resveratrol was further confirmed by FABMS. It gave peaks at *m/z* 227 corresponding to $[M-H]^-$ molecular ion and at *m/z* 137 indicating the loss of a trihydoxyphenyl unit. The ^1H and ^{13}C NMR values obtained for **2** were identical to those found for resveratrol (*31*).

Compound **1** showed absorption maxima at 224 and 313 nm, identical to those found for resveratrol. In a negative ion mode spectrum the molecular peak was

Table 1. ^{1}H and ^{13}C NMR Data of Compounds 3−5 in CD_3OD[a]

	3		**4**		**5**	
carbons	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
2	5.89, s	93.3	6.00, s	94.8	5.87, s	93.5
3		60.9		61.2		61.6
4		177.0		181.1		176.9
5		156.3		156.0		156.2
6	5.95, d, $J = 1.5$	97.4	5.90, d, $J = 1.5$	97.4	5.97, d, $J = 1.5$	97.0
7		162.0		162.2		162.0
8	6.16, d, $J = 1.5$	91.0	6.21, d, $J = 1.5$	90.6	6.16, d, $J = 1.5$	90.4
9		164.6		162.9		164.6
10		105.0		107.5		104.8
1′		127.5		127.7		128.0
2′	6.93, d, $J = 8.3$	128.2	6.99, d, $J = 8.3$	127.9	6.92, d, $J = 8.3$	128.2
3′	6.70, d, $J = 8.3$	115.9	6.52, d, $J = 8.3$	115.1	6.70, d, $J = 8.3$	116.0
4′		159.1		158.3		158.7
5′	6.70, d, $J = 8.3$	115.9	6.52, d, $J = 8.3$	115.1	6.70, d, $J = 8.3$	116.0
6′	6.93, d, $J = 8.3$	128.2	6.99, d, $J = 8.3$	127.9	6.92, d, $J = 8.3$	128.2
1″		137.4		138.1		137.1
2″		117.9		117.1		117.5
3″		155.8		155.0		155.8
4″	6.42, d, $J = 1.5$	98.4	6.36, d, $J = 1.5$	97.7	6.41, d, $J = 1.5$	98.0
5″		159.9		159.2		159.7
6″	6.94, d, $J = 1.5$	108.3	6.65, d, $J = 1.5$	106.7	6.96, d, $J = 1.5$	107.7
1‴		134.3		130.5		129.7
2‴	6.38, s	107.2	7.24, d, $J = 8.3$	129.3	7.14, d, $J = 8.3$	129.3
3‴		152.0	6.81, d, $J = 8.3$	116.8	6.73, d, $J = 8.3$	116.5
4‴		137.3		158.7		158.8
5‴		152.0	6.81, d, $J = 8.3$	116.8	6.73, d, $J = 8.3$	116.5
6‴	6.38, s	107.2	7.24, d, $J = 8.3$	129.3	7.14, d, $J = 8.3$	129.3
α	6.95, d, $J = 16.2$	122.8	6.53, d, $J = 16.2$	122.8	6.96, d, $J = 16.2$	120.9
β	6.93, d, $J = 16.2$	132.9	6.73, d, $J = 16.2$	131.4	7.05, d, $J = 16.2$	132.5
OMe	3.82	60.8				

[a] Assignments confirmed by DQF−COSY, HSQC, and HMBC experiments.



4 5

Figure 3. Computer representation of compounds **4** (yuccaol A) and **5** (yuccaol B).

found at *m*/*z* 273 and the second peak at *m*/*z* 137 indicated the loss of a $C_7H_5O_3$ fragment. Analysis of ^{1}H and ^{13}C NMR data of the stilbene derivative **1** indicated the same ring A as in resveratrol and allowed us to deduce for ring B a 3′,5′-dihydroxy-4′-methoxyphenyl structure. In particular, the location of the OMe group at C-4′ was derived from the HMBC spectrum, which showed a correlation between the proton signal at *δ* 3.83 (3H, s, OCH_3) and the carbon resonance at *δ* 136.2 (C-4′). On the basis of these findings the structure of **1** was determined as *trans*-3,3′,5, 5′-tetrahydroxy-4′-methoxystilbene (Figure 1). This compound was identified for the first time in the stem of *Phoenix dactylifera* (*32*) and its presence was later confirmed in the roots of *Cassia pudibunda* (*33*), but it was not identified before in yucca bark. The synthesis of this compound was also performed (*32*).

The ^{13}C NMR spectrum of compound **4** showed 25 signals, four of which had double intensity (Table 1). On the basis of ^{13}C DEPT NMR, these signals were assigned to one carbonyl carbon (*δ* 181.1), seven phenolic carbons (*δ* 162.9, 162.2, 159.2, 158.7, 158.3, 156.0, 155.0), five aromatic quaternary carbons (*δ* 138.1, 130.5, 127.7, 117.1, 107.5), one aliphatic quaternary carbon (*δ*

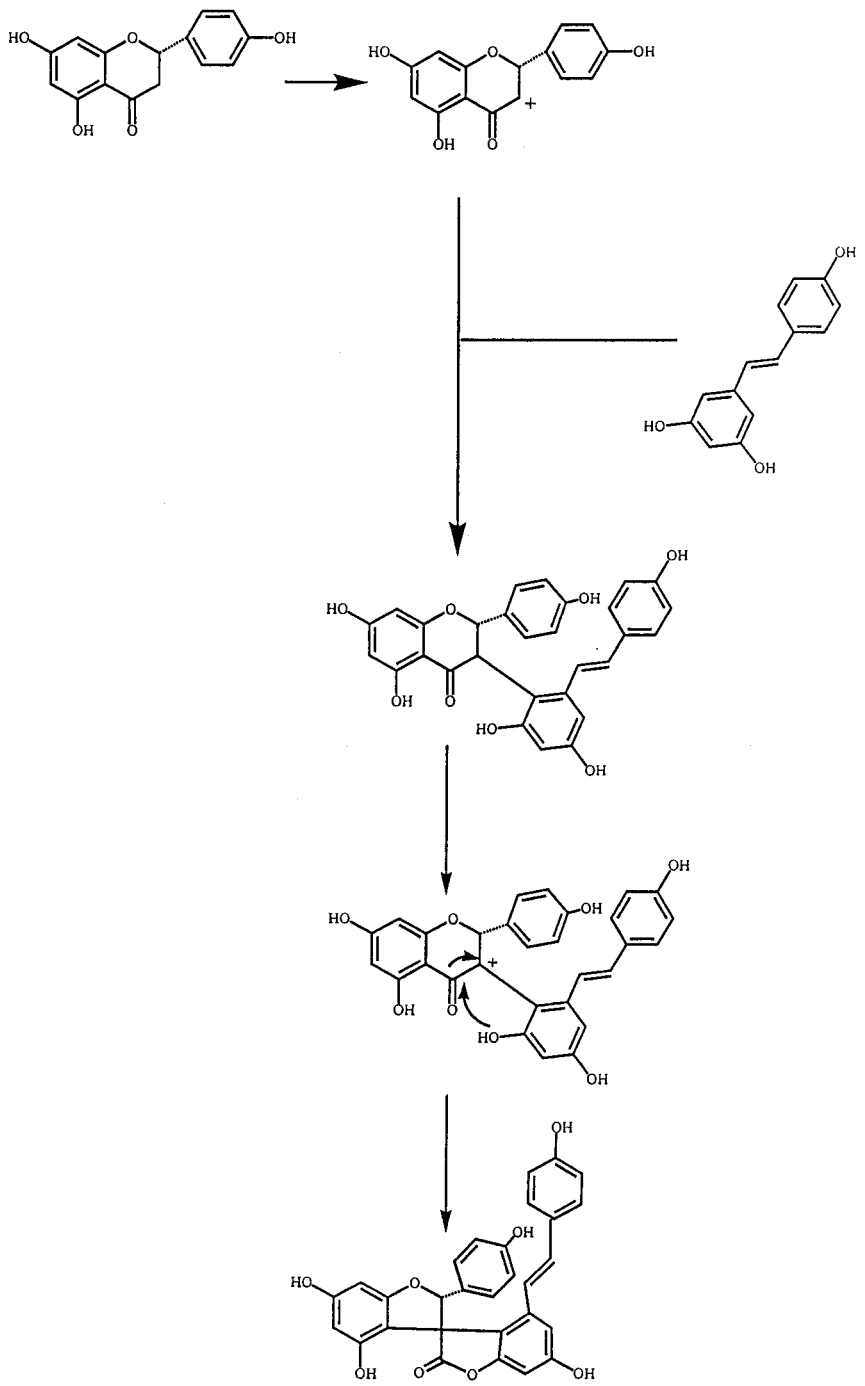


Figure 4. Proposed biosynthetic pathway for yuccaols A−B.

61.2), and fifteen methine carbons (δ 131.4, 129.3 × 2, 127.9 × 2, 122.8, 116.8 × 2, 115.1 × 2, 106.7, 97.7, 97.4, 94.8, 90.6). The ^{1}H NMR spectrum of **4** (Table 1) displayed four doublets at δ 7.24 (2H, d, J = 8.3 Hz), 6.99 (2H, d, J = 8.3 Hz), 6.81 (2H, d, J = 8.3 Hz), and 6.52 (2H, d, J = 8.3 Hz), typical of *ortho*-coupled aromatic protons. Also evident were two signals at 6.73 (1H, d, J = 16.2 Hz) and 6.53 (1H, d, J = 16.2 Hz), indicative of a *trans* double bond, four signals at 6.65 (1H, d, J = 1.5 Hz), 6.36 (1H, d, J = 1.5 Hz), 6.21 (1H, d, J = 1.5 Hz), and 5.90 (1H, d, J = 1.5 Hz), attributable to two pairs of *meta*-coupled protons and a singlet at δ 6.00. The DQF−COSY experiment permitted the couplings between the signals at δ 5.90 and 6.21, 6.36 and 6.65, 6.52 and 6.99, and 6.81 and 7.24 to be established. The HSQC experiment clearly showed correlations: δ_H 5.90 → δ_C 97.4, δ_H 6.00 → δ_C 94.8, δ_H 6.21 → δ_C 90.6, δ_H 6.36 → δ_C 97.7, δ_H 6.52 → δ_C 115.1, δ_H 6.53 → δ_C 122.8, δ_H 6.65 → δ_C 106.7, δ_H 6.73 → δ_C 131.4, δ_H 6.81 → δ_C 116.8, δ_H 6.99 → δ_C 127.9, and δ_H 7.24 → δ_C 129.3. From the above-reported data it was possible to deduce the occurrence of a monosubstituted phloroglucinol ring and two *para*-hydroxy substituted phenyl rings, one of which belonged to a stilbene moiety. The complete elucidation of the structure of **4** was achieved by the HMBC experiment, which showed the correlations reported in Figure 2. On the basis of the observed correlations it was possible to deduce that **4** was made up of two fragments: one of 15 carbons probably derived from a flavonoid skeleton and the other one of 14 carbons identified as a *trans*-3,4′,5-trihydroxystilbene substituted at position 2, by comparison of NMR data with

those of resveratrol (*31*). The manner of the attachment of the stilbene portion to the residual C_{15} unit could be unambiguously derived from the long-range correlations between the proton signal at 6.00 and the carbon resonances at 61.2, 117.1, 127.7, 127.9, and 181.1, which allowed us to deduce for **4** the spiro-structure including a δ-lactone function as shown in Figure 1.

Comparison of ^{1}H and ^{13}C NMR data of **5** to those of **4** clearly indicated structural similarity between the two compounds (Table 1). The main differences were in the ^{1}H NMR spectrum, especially the chemical shifts of H-2 (δ 5.87 in **5** vs 6.00 in **4**), H-α (δ 6.96 in **5** vs 6.53 in **4**), H-β (δ 7.05 in **5** vs 6.73 in **4**), H-6″ (δ 6.96 in **5** vs 6.65 in **4**), and in the ^{13}C NMR spectrum the C=O (δ 176.9 in **5** vs. 181.1 in **4**), C-2 (δ 93.5 in **5** vs 94.8 in **4**), C-α (δ 120.9 in **5** vs 122.8 in **4**), C-β (δ 132.5 in **5** vs 131.4 in **4**), C-9 (δ 164.6 in **5** vs 162.9 in **4**) and C-10 (δ 104.8 in **5** vs 107.5 in **4**) resonances. Analysis of the observed shifts prompted us to hypothesize that the difference between the two compounds should be confined to the stereochemistry at C-3. The ROESY experiment of compound **4** clearly showed nOe effects between H-2′ and H-α, H-β, H-2‴ whereas the ROESY spectrum of compound **5** displayed nOe effects between H-2 and H-α, H-β. Inspection of molecular models and computer representations of the two molecular models differing in the stereochemistry at C-3 (Figure 3) suggested that the nOe effects observed for compound **4** were expected for the isomer having the *p*-hydroxyphenyl ring of the C_{15} unit and ring A of the stilbenic portion on the same side, and nOe effects elicited in **5** were in good agreement with the location of H-2 on the same side as ring A of the stilbene portion. Thus, the relative stereochemistries reported in Figure 1 were assigned to compounds **4** and **5**, which were given the trivial names yuccaol A and B, respectively.

Analysis of ^{1}H and ^{13}C NMR data of compound **3** in comparison with those of **5** (Table 1) suggested that the two compounds differed only in the stilbene portion. In particular the signals of the *p*-hydroxy substituted aromatic ring of the stilbene portion are typical of a 3,5-dihydroxy-4-methoxy aromatic ring. The location of the methoxy group at C-4‴ was established on the basis of the long-range correlation between the carbon signal at δ 137.3 (C-4‴) and the proton signal at δ 3.82 (OCH_3). Thus, the structure reported in Figure 1 was assigned to compound **3** and named yuccaol C.

The spiro-structures of compounds **3**−**5** are very rare. The C_{15} portion occurring in **3**−**5** has been previously reported in larixinol, a spirobiflavonoid isolated from *Larix gmelini* (*34*), which is made up of two C_{15} units of flavonoid origin. For larixinol a biogenetic pathway has been proposed, which associates the biogenesis of larixinol to that of the C-3 → C-8′ linked Garcinia group of biflavonoids. The suggested biogenetic pathway incorporates the hypothesis that both larixinol and garcinia biflavonoids originate from the attachment of a flavan unit (epiafzelechin in the case of larixinol) to a carbocationic intermediate in the oxidative flavanone−flavonol conversion (*34*). On the basis of this hypothesis, we can suppose that yuccaols A−C derive from the attachment of the stilbenic derivative (*trans*-resveratrol in the case of **4** and **5**, *trans*-3,3′,5,5′-tetrahydroxy-4′-methoxystilbene in the case of **3**) to the carbocationic intermediate of the oxidative flavanone−flavonol conversion according to the proposed scheme (Figure 4). The different stereochemistry at C-3 in **4** and **5** could be explained by the involvement of the C-3 carbocationic intermediate in the proposed biogenetic pathway.

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